Chapter 3

Developmental Toxicity I: Perinatal Manifestations

3.1 Introduction

This chapter reviews the evidence on the impact of ETS exposure during pregnancy on: 1) fetal growth, including decreased birthweight, growth retardation, or prematurity; 2) fetal loss, including spontaneous abortion and perinatal mortality; and 3) congenital malformations. The review of each of these three categories of outcome begins with a brief discussion of studies which assessed the effect of active smoking by the mother during pregnancy. Although the impact of active smoking on development is not the topic of this document, it provides a context within which to consider the possible effects of ETS exposure. The brief discussion of active smoking effects is followed by detailed descriptions of epidemiologic studies of ETS exposure and the specific outcome. Pertinent animal studies are then described. Each review concludes with a discussion of the overall evidence from animal and epidemiological studies for adverse impacts of ETS.

3.2 Fetal Growth

By far the majority of epidemiologic studies on perinatal effects of ETS exposure have investigated fetal growth, and most of these studies have focused on birthweight. Technically, fetal growth should be measured by comparing size at a number of time intervals. However, measures at birth are commonly used as surrogates. Those measures include mean birthweight, low birthweight (LBW) (<2500 grams), and intra-uterine growth retardation (IUGR), which is defined as less than the tenth percentile of weight for gestational age. The LBW category includes infants that are growth retarded, or small for their gestational age, as well as infants who are not growth retarded, but were born prematurely. These may result from different etiologies**,** therefore some investigators examine LBW (or IUGR) in term births only; preterm births are also examined as a separate category. Examining IUGR over the range of gestational ages (22-42 weeks) provides more power than examining only LBW at term. Because a portion of the "normal" population will fall into the IUGR category, however, there is some question as to what extent this categorization measures "abnormality" (Stein and Susser, 1984).

3.2.1 Overview of Fetal Growth and Maternal Smoking During Pregnancy

Smoking by the mother during pregnancy has long been considered an important independent risk factor for decreased infant birthweight. The association was first reported in 1957, and the weight of evidence indicates a causal effect (see Stillman *et al.*, 1986; U.S. DHHS, 1980). Infants of active smokers typically have a mean birthweight 150-200 grams less than those of nonsmokers, and are twice as likely to be of low birthweight. The reduction in birthweight does not appear to be due to more pre-term births; rather, infants are growth retarded at all gestational ages. There is evidence that other growth measures, such as length and head circumference, are also reduced in infants of smokers.

The effect of smoking may result primarily from exposure to carbon monoxide and nicotine. Carbon monoxide can cause fetal hypoxia, for which the fetus is physiologically unable to adequately compensate (see Stillman *et al.*, 1986; U.S. DHHS, 1980). Nicotine leads to decreased uteroplacental perfusion and also crosses the placenta to affect the fetal cardiovascular system, as well as the gastrointestinal and central nervous systems (Stillman *et al.*, 1986). Other constituents of cigarette smoke (*e.g.*, toluene, cadmium) have been shown to produce fetal growth deficits (Donald et al., 1991; OEHHA, 1996). All of these compounds are also present in ETS.

3.2.2 Human Studies of Fetal Growth and ETS Exposure

Many of the early epidemiological studies of ETS exposure and fetal growth did not adjust for confounders. When examining fetal growth, a number of co-variables should be considered initially, including: maternal age, race, parity or prior reproductive history, maternal smoking, socioeconomic status and/or access to prenatal care. Few studies have information on maternal stature or weight gain, but these are also important determinants of fetal weight, as are certain illnesses, complications of pregnancy, and gender of the infant. Gestational age at delivery is the strongest predictor of birthweight. Multiple births are much more likely to result in lower birthweights, so study populations are often limited to singleton births. Although many factors may be related to birthweight, their distribution by ETS exposure status must vary in order them to confound an association of ETS and birthweight. A confounder in one study population is not necessarily a confounder in another.

The descriptions of the epidemiological evidence on fetal growth are presented by exposure measure (*i.e.*., home exposure, home and work exposure, biomarkers). The numerous studies on exposure to ETS in the home are presented in two different subsections, one on mean birthweight, the other on growth retardation or prematurity.

3.2.2.1 Home ETS Exposure and Mean Birthweight

All but one of the studies of the impact of ETS exposure in the home on mean birthweight found a decrement in mean birthweight, although in about half the decrement was small (Table 3.1; Figure 3.1, top). A few early studies found little effect, but none of them controlled for confounders or performed much statistical analysis. Of the studies conducted in the last decade, seven found decrements ranging from 30 to 200 grams while four found very little association with paternal smoking, and weight decrements of less than 20 grams. Two of the four which found little association were based on selected populations (*e.g.*, offspring of twins); this may have introduced some bias and affected the generalizability of the results (Magnus *et al.* 1984; MacArthur and Knox, 1987). Similarly one which found the greatest weight decrement also studied a select population (Schwartz-Bickenbach *et al.*, 1987). The studies are described in chronological order below.

MacMahon et al. (1966)

MacMahon *et al.* (1966) studied a large sample of live births by sending their mothers a questionnaire to ascertain parental smoking habits during the calendar year in which the pregnancy started. Overall, the study found an 86.8 gram decrement associated with any paternal smoking for female infants, with a slightly lower decrement for male infants (-78 grams). Limiting the analysis to nonsmoking mothers, a crude 22 gram decrement for female infants was associated with paternal smoking and a 20 gram decrement for males (Table 3.1). There was no evidence of a dose-response effect. Paternal pipe or cigar smoking was associated with similar decrements, on the order of 20-30 grams.

Comstock and Lundin (1967)

In a study of Maryland vital records, Comstock and Lundin (1967) noted that the mean birthweight of infants with smoking fathers and nonsmoking mothers was 42 grams less than that of infants whose parents both did not smoke. In addition to a lack of statistical analysis, this study ascertained smoking status from a special census and thus was not specific to the pregnancy.

Underwood et al. (1967)

Underwood *et al.* (1967) published a large study of newborns delivered in naval installations worldwide. The greatest limitation of this study is the unusual ascertainment of smoking status; it was obtained from the physician attending the birth in the various labor and delivery rooms. Examining infants whose mothers did not smoke, the authors found that mean birthweight was decreased only 3-7 grams depending on the amount smoked by the father. However, from a figure in the report it appeared that heavy (>30 cigarettes/day) paternal smoking had a greater effect on birthweight in infants born before 35 weeks (about a 100 g decrement), although the authors did not comment on this. No confounders were considered in this analysis.

Borlee et al. (1978)

Borlee *et al.* (1978) examined birthweight and body measurements of infants from a hospital-based case-control study of congenital malformations conducted in Belgium. The authors appear to include the malformed children in most of the analyses, which may make the results less generalizable. Mean birthweight of infants of non-smoking mothers was decreased by 228 grams if the father smoked before conception. Among infants of smoking mothers, those with smoking fathers were heavier than those with nonsmoking fathers, but this finding is based on only 14 infants with nonsmoking fathers and smoking mothers, so is not reliable. Length and head circumference varied little by paternal smoking status. Using the entire study group for an analysis of variance with a few co-variables (malformation, prematurity, maternal tobacco use), there was an association between paternal smoking and birthweight ($p<0.06$), but the adjusted difference was not presented. Other important potential confounders identified by the authors were not taken into account. The magnitude of effect of ETS exposure seems implausibly large, but the decrement in mean birthweight associated with active maternal smoking, among infants of nonsmoking fathers, was much greater still (*e.g.*, - 561 grams, crude difference).

Magnus et al. (1984)

Magnus *et al.* (1984) studied causes of variations in birthweight in offspring of adult twins in Norway. This is a select population (offspring of parents who are twins) and the generalizability of the results is unclear. The authors assumed that smoking status at interview reflected habits during childbearing years. There are few data on this topic, for fathers in particular. However, some decrease in smoking during the 10-15 years since some of the study births would be expected. Fathers who smoked during the target pregnancy, but not at the later interview, would be included as nonsmokers, diluting any effect. In a bivariate regression, paternal smoking was associated with a 48 gram decrement in birthweight ($p<0.01$). In a multiple regression analysis that included maternal smoking and some other covariates, paternal smoking was only associated with a 5 gram decrement (Table 3.1). Maternal smoking remained significantly associated with birthweight decrements.

Karakostov (1985)

In a study conducted in Bulgaria, Karakostov (1985) reported an 84 gram weight decrement in infants of women exposed to ETS during pregnancy compared to infants whose parents were both nonsmokers. The measure of variability in birthweight is unclear; it is presented as the standard deviation, but because it is so small (*i.e.*, 60 to 80 grams) it appears to be the standard error. Assuming the latter, the confidence interval is wide (95% CI = -280 to 111). Mean length was decreased by about one-half centimeter. No confounders were controlled.

Rubin et al. (1986)

In 1986, Rubin *et al.* reported a positive association between birthweight and paternal smoking which spurred many of the subsequent studies. Five hundred Danish women were interviewed shortly after delivery regarding smoking by fathers and other household members. Births were all greater than 2000 grams and 35 weeks gestation, so they represent a relatively healthy group *a priori*. Maternal and paternal smoking were highly correlated; both variables were examined together in regression models. Adjusting for many covariables (but not maternal height or weight), the independent decrement in birthweight per cigarette (or cigar or pipe bowl) smoked daily by the father was 6.1 grams ($p<0.03$). This yields about a 120-gram decrement for smoking a pack of cigarettes each day. The association appeared to be greatest in the lower social classes, although no interaction terms were included in the regression models. The decrement seen with maternal smoking was 9.2 grams per cigarette per day (adjusted for paternal smoking and other variables).

MacArthur and Knox (1987)

A second study with a highly selected sample was reported in a letter to *Lancet.* MacArthur and Knox (1987) focused on 180 women who reported that they stopped smoking during pregnancy, a group unlikely to be representative of nonsmokers. Some data related to paternal smoking were provided, but not information about the study from which the data were derived or the statistical methods used. As maternal and paternal

smoking are usually correlated, it was somewhat surprising that there was no reported difference in the mean amount smoked before pregnancy by women whose partners smoked compared to women whose partners did not. The authors found only a 14 gram decrement in mean birthweight if the father smoked. They indirectly standardized the birthweight distributions of each paternal smoking group for maternal height and parity, and for sex and gestational age of the infant, and noted a 123 gram excess if the father smoked. However, both groups had an "excess" birthweight (100 grams among infants of nonsmoking fathers and 223 grams among those of smoking fathers) relative to an unspecified comparison group. The excess in both groups may indicate that women who stop smoking adopt other healthy behaviors that contribute to a healthier outcome, or that this group of women is not comparable to the general population.

Schwartz-Bickenbach et al. (1987)

Schwartz-Bickenbach *et al.* (1987) reported on a small study in Berlin of mothers who intended to breast feed their infants, comparing infant development in pairs where one mother smoked during pregnancy and the other did not. Among the nonsmoking women (n = 54), about half had a spouse who smoked. Those infants with smoking fathers and nonsmoking mothers weighed on average 205 grams less than infants whose parents did not smoke (Table 3.1). This is a large decrement in weight, but the decrement associated with maternal smoking was on the order of 400 grams. There was no statistical comparison of these weight differences. Assuming that the variability index in the published table is the standard deviation, the p-value for a t-test of the weight decrement associated with exposure to ETS would be 0.095. There was no difference in head circumference by parental smoking habits but there were slight differences in body length. The magnitude of effect of paternal smoking was about half that of maternal smoking at 1.1 cm (95% CI = -2.3 to 0.1). This population was highly selected and no confounding variables were controlled.

Campbell et al. (1988)

Campbell *et al.* (1988) examined the effect of ETS exposure in a population-based sample of births that occurred in Southampton, England. The mothers were interviewed one month after delivery. In infants of maternal nonsmokers the authors found a crude weight difference of -73 grams associated with paternal smoking. In a multiple regression analysis adjusting for maternal smoking, age, alcohol consumption and social class, current paternal smoking status was associated with a 113 gram decrement in birthweight, about one-half the effect of maternal smoking (-253 grams) in all births (Table 3.1). The greatest decrement in weight was seen when both parents smoked. This appears to be well-conducted study, but the inclusion of maternal smokers in the regression analysis complicates its interpretation.

Brooke et al. (1989)

Brooke *et al.* (1989) reported a thorough prospective study of factors influencing birthweight, which was conducted in London. Smoking habits were ascertained at registration for prenatal care and at 28 and 36 weeks gestation. The ETS exposure

variable was defined as any smokers (other than the mother) in the household. Birthweight was expressed as a ratio of observed birthweight to expected mean birthweight for gestational age. That ratio was then adjusted for parity, maternal height and infant sex. In infants of nonsmoking mothers, those with ETS exposure had a 0.5% reduction in the birthweight ratio; among infants of smoking mothers with ETS exposure, there was a 1% reduction. This corresponded to a difference in mean birthweight (adjusted to 40 weeks) associated with ETS exposure of 18 grams in nonsmokers and 39 grams in smokers.

Chen et al. (1989)

Chen *et al.* (1989) reported a retrospective study of all births occurring during a 6-month period in 1981 in an area of Shanghai, China. One advantage of this study is that none of the interviewed mothers were smokers; disentangling the correlation of spousal smoking habits is therefore not an issue. ETS exposure estimates were based on the daily cigarette consumption by the spouse and other family members. The proportion of mothers exposed to ETS (72%) was higher in this study than in most other studies. Mean birthweight was decreased only 9-11 grams, depending on the amount smoked by the spouse (1-9 or $\geq$10 cigarettes/day) ($F=0.3$, $p=0.74$) and was decreased 4-15 grams, depending on the amount smoked by all family members ($F=0.7$, $p=0.92$). The authors stated that adjusting for multiple confounders (gender, parity, education, maternal age and income) did not change the results. Two potential confounders not available were maternal height and weight, which may not be as variable in China as in the U.S..

Saito (1991)

A study from Japan (Saito, 1991) examined the smoking habits of about 3,000 couples who brought their infants into a large Tokyo medical center for care during 1987. The majority of women did not smoke during their pregnancy and about half the fathers smoked. Among infants whose father smoked but whose mother did not smoke during pregnancy, there was a decrement in mean birthweight of 33.4 grams ($p<0.05$) compared to infants of nonsmoking parents (Table 3.1). Among infants whose parents both smoked, the mean birthweight was further decreased 66 grams (or about 100 grams total). The author found a dose-response effect by amount the father smoked, with a weight decrement of 111 grams ($p<0.01$) among infants of fathers who smoked 40 or more cigarettes per day. In this later analysis the author appears to include couples in which the mothers also smoked. Such couples do not comprise a large portion of the sample (perhaps 8%), but nevertheless, a direct effect of maternal active smoking may have influenced the dose-response results. The author further found that the weight decrement was slightly greater among female (126.5 grams) than among male infants (94.3 grams) of heavily smoking fathers. This gender differential was even more striking for weight decrements seen with active maternal smoking. In addition to including smoking mothers in some analyses, this study is limited because it did not control for any confounders, despite reporting that smoking levels varied by age, education and paternal occupation.

Mathai et al. (1990 and 1992)

Mathai *et al.* (1990 and 1992) conducted two studies in different populations and obtained similar results (Table 3.1). The first study was conducted prospectively among 285 white women attending a prenatal clinic in Liverpool, England in 1987 (Mathai *et al.,* 1990). Fifty-four women (19%) were nonsmokers who lived with a smoker and were thus considered exposed to ETS. Their infants had a mean weight decrement of 66 grams compared to non-exposed nonsmokers; this was not statistically significant, but it was based on small numbers. No confounders were controlled in the analysis. A subsequent improved study (Mathai *et al.,* 1992), designed specifically to examine ETS exposure in a population with few women smokers, included 994 mothers of singletons born in 1990 in Vellore, India. The timing of interview was not specified, but appears to be after delivery. None of the women used tobacco, but 52% lived with smokers and were considered to be exposed to ETS. ETS exposure was crudely associated with a 55 gram decrement in mean birthweight. Adjusting for multiple confounders (maternal age, height, parity, social class, gestation, and infant sex), the mean decrement was 63 grams (p=0.015). No information on a dose-response relationship was available.

Zhang and Ratcliffe (1993)

Zhang and Ratcliffe (1993) examined the effects of paternal smoking on livebirths who had served as controls in a study of birth defects. Among singleton term births of nonsmoking women in Shanghai, there was a crude weight decrement of 26 grams associated with paternal smoking. Adjustment for parity, maternal age, gestational age and mother's occupation by multiple linear regression yielded a decrement of 30 grams (95% CI= -66 to 7). There was a non-linear dose-response trend by amount smoked, with greater adjusted weight decrements seen up to 19 cigarettes/day, but an increase in weight at higher levels (20 or more cigarettes/day) (Table 3.1). The confidence interval at the higher level of paternal cigarette consumption overlapped with the decrements estimated at lower smoking levels. The non-monotonic trend in dose-response may be due to chance, or inaccuracy in reporting of paternal amount by their spouses, or a confounding variable not taken into account. The paternal smoking ascertained appeared to reflect usual smoking status, not necessarily that during pregnancy.

Martinez et al. (1994)

Martinez *et al.* (1994) studied enrollees of the Tucson Children's Respiratory Study, conducted in a large health maintenance organization in Tucson, Arizona. Information (including birthweight) was obtained by nurses while the mothers were in the hospital following the birth. Each parent was given a questionnaire to answer about his or her own smoking habits, and the person's current smoking habit was used to estimate the amount smoked during pregnancy, because it was obtained so soon after delivery. Among the 992 non-smoking mothers, infant birthweight significantly decreased with increasing paternal smoking; infants whose fathers smoked more than 20 cigarettes per day had a mean weight decrement of 88 grams. Maternal smoking of more than 20 cigarettes per day was associated with an average 250 gram decrement. In a multiple regression analysis adjusting for gestational age, gender, race, parity, education, and maternal age, paternal

smoking was associated with a 34 gram decrement for each additional 10 cigarettes smoked per day (Table 3.1). Duration of pregnancy was not affected by the smoking habit of either parent. Cotinine measured in cord blood for a sub-sample indicated that perhaps 1.5% of the women were smokers misclassified as non-smokers. The two women thus misclassified had non-smoking spouses, so it is not clear that such misclassification would necessarily lead to finding a greater weight decrement with ETS exposure, which is a common criticism of studies of ETS. Detection of cord blood cotinine was reported to be strongly correlated with the number of cigarettes smoked by the father. Minor limitations of this study are the lack of information on other potential confounders, such as alcohol consumption, and the use of smoking habits reported after delivery to represent smoking during pregnancy; however, it is unlikely that women who smoked during pregnancy would quit after delivery.

3.2.2.2 Home ETS Exposure and Low Birthweight, Growth Retardation or Prematurity

Several of the studies mentioned above, as well as some additional ones, examined the impact of spousal smoking status on low birthweight, growth retardation or prematurity (Table 3.2; Figure 3.2, top). These studies are described below. Low birthweight was defined as less than 2500 g in all but one study. For the most part, odds ratios or similar measures indicating ETS impacts were of a magnitude of 1.5 or less; some studies found evidence of dose-response trends.

Underwood et al., (1967)

In a large study of births in naval institutions (discussed above), information on parental smoking status was obtained from the attending physician (Underwood *et al.*, 1967). The authors reported little difference in rates of LBW or prematurity (<36 weeks) by amount smoked by the father, among births of nonsmoking mothers (Table 3.2). Based on the data provided, we calculated an odds ratio of 0.9 for any paternal smoking and 1.05 for smoking over 30 cigarettes per day for either LBW or prematurity (Table 3.2). The reliability of the smoking information is unclear, particularly given the means of ascertainment of smoking status and the number of institutions involved. However, the finding of a dose-response relationship for maternal smoking and LBW, as expected, provides some confidence in the classification of smoking status. No confounders were controlled.

Terris and Gold (1969)

A study (Terris and Gold, 1969) sometimes cited in the literature has not been included in the tables or figures. It was a case-control study of LBW among black births, with controls matched by infant sex and birth order, as well as by maternal age and marital status. The main problem with the study is that no separation or control of maternal smoking was attempted in considering paternal smoking. Smoking was more frequent among mothers of LBW cases, but paternal smoking status varied little between cases and controls.

Yerulshalmy (1971)

Using data from the large, prospective Child Health and Development Studies conducted among members of the Kaiser Foundation Health Plan, Yerulshalmy (1971) examined the effect of parental smoking on fetal growth. He found that the proportion of LBW infants from pregnancies in which the husband smoked was increased significantly compared to those in which the husband did not smoke. When stratified by maternal smoking status, this association was apparent only among pregnancies in which the mother also smoked; the highest rates of LBW occurred where both parents smoked during pregnancy. Calculating a rate ratio for LBW and paternal smoking yielded 1.4 among smoking mothers (p reported <0.05) and around 1.0 among nonsmoking mothers. The raw data were not presented in this paper, nor was there any control for confounding.

Mau and Netter (1974)

Mau and Netter (1974) reported data on parental smoking and a number of fetal growth parameters from a large, prospective study conducted in Germany. They examined rates of IUGR, prematurity, and LBW by amount smoked by the father among 3,696 pregnancies of nonsmoking mothers. About 44% of these pregnancies were exposed to paternal smoking. The investigators found slight increases in each outcome among infants of fathers who smoked more than 10 cigarettes per day, but none of the chi-square tests for the distribution of amount of paternal smoking by each pregnancy outcome was statistically significant. The authors standardized the "value of expectation" for paternal age, so it is not clear whether the rates and numbers in the tables represent raw data and can be used for confidence interval calculations (as we did in Table 3.2). Nevertheless, focusing on the fathers who smoked more heavily, the rate ratios were 1.2 for IUGR and prematurity and 1.4 for LBW (Table 3.2). No confounders other than paternal age were controlled in these analyses.

Nakamura et al. (1988)

Nakamura *et al.* (1988) conducted a prospective study of pregnancies during 1984-86 in Osaka, Japan. The authors noted that the percentage of males who smoked (67%) was one of the highest in the developed world, whereas few females smoked (13%), so the rate and intensity of ETS exposure may be greater than elsewhere. They examined the rates of LBW, LBW at term (also referred to as small for gestational age, or SGA) and prematurity. Focusing on nonsmoking mothers only, the crude rates for positive paternal smoking status were increased for LBW (OR=1.5), and slightly for preterm and SGA births (OR=1.2). The investigators adjusted for a variety of potential confounders in a logistic regression model. The adjusted relative risk for LBW was 1.4 (95% CI= 0.9 - 2.2) (Table 3.2). Because they had no information on ETS exposure at work, the investigators also performed an analysis in non-working women so that exposure would be less likely to be misclassified. The adjusted relative risk for home exposure and LBW in this group was significantly elevated: 1.7 (95% CI= 1.0 - 2.9). The authors noted that residence size was small in this area, which may have resulted in ETS exposures of relatively high intensity.

Chen et al. (1989)

The retrospective study reported by Chen *et al.* (1989) discussed above, which was conducted in Shanghai, also reported a high prevalence of male smokers (58%) and no female smokers. The authors found no evidence of a dose-response relationship of amount smoked by the father or by all household members to rates of LBW, nor did consideration of a few confounders change the results (adjusted data not presented). Combining results across all categories of paternal smokers, we calculated a crude odds ratio of 1.5 (95% CI = 0.75 - 3.2) for LBW.

Saito (1991)

In the study of Japanese couples discussed above, Saito (1991) examined the rate of "small for dates" (SFD), which was defined as a weight less than 1.5 standard deviations below an established population mean. The rates of SFD were slightly increased among infants of smoking fathers and nonsmoking mothers (calculated OR=1.3; $p \leq 0.05$) (Table 3.2). The only stratified analysis conducted was by paternal education, which appeared to confound slightly the relationship of SFD and paternal smoking. Paternal smoking of 20 or more cigarettes per day increased the rate of SFD within both categories of paternal education, by about 40% ($p<0.05$), compared to infants of fathers who smoked less or not at all. The rate of prematurity did not vary by paternal smoking status.

Mathai et al. (1992)

The Mathai *et al.* (1992) study of 994 East Indian births in Vellore discussed above also examined prematurity and LBW by whether the mother lived with a smoker. The authors reported that 52% of births were thus exposed to ETS. The outcome variable was limited to lighter (<2000 grams) babies than the usual definition for LBW, and the authors found no difference in these rates of LBW by mother's ETS exposure (Table 3.2). The rate of prematurity was increased somewhat with ETS exposure (OR = 1.6, 95% CI = 0.82 - 2.9). No confounders were considered in the analysis of these outcomes.

Zhang and Ratcliffe (1993)

In the Zhang and Ratcliffe study (1993) of infants of nonsmoking Chinese women discussed previously, the rates of LBW at term and IUGR were similar whether the father was a smoker or a nonsmoker (crude RRs = 1.07 and 1.11, respectively) (Table 3.2). No consistent dose-response trend was seen with amount smoked. No confounders were considered in this analysis.

3.2.2.3 Home and Work ETS Exposure and Fetal Growth

Fewer studies have examined fetal growth in relation to ETS exposures defined by something other than paternal smoking status, so all outcomes are grouped together in this subsection. All of these are recent and thus tend to reflect today's higher methodologic standards. Four studies published in 1995 are reviewed as an addendum at the end of this section. Generally, these studies found associations between ETS exposure and fetal size of smaller but more consistent magnitudes than the paternal smoking studies (Table 3.3).

Martin and Bracken (1986)

In 1986, Martin and Bracken published results from a widely cited prospective study of 3,891 pregnancies ending in livebirths between 1980-82 in Connecticut (Table 3.3). Passive smoking (ETS exposure) was defined as being exposed to someone else's cigarette smoke for at least two hours per day, either at home or at work. However, it is not clear whether this was asked as a "yes/no" question or whether data were pooled from a few questions. Among all infants of nonsmokers, ETS exposure was crudely associated with a 61 gram decrement in mean birthweight (p=0.005) and a slightly increased rate of LBW (RR=1.3). These associations with ETS exposure were not seen in infants of maternal active smokers. There was no association of prematurity with ETS exposure. Stratifying by gestational age, there was a significant association in nonsmokers who had term pregnancies (OR for LBW: 2.7; weight decrement: 85 grams), which the authors interpreted as indicating an effect on growth retardation. Adjustment for confounders by multiple regression yielded a mean weight decrement of 24 grams (p=0.20) and an odds ratio for LBW of 2.2 (95% CI = 1.1 - 4.5) among term births.

One criticism of this paper has been that the authors included only confounders that were significant at the p= 0.1 significance level in a stepwise regression model. This approach is now considered inappropriate because confounding should not be assessed by a significant association with the outcome variable, but by the magnitude of change in the odds ratio if that covariate is not taken into account (Rothman, 1986). Nevertheless, the variables usually considered important were included (*i.e.*, maternal age, parity and ethnicity). The authors also included gestational age in the models, even though they were only examining term births. The authors stated that maternal weight gain was not included because it was missing for about 25% of respondents. In an analysis of those for whom the information was available, this variable did not appear to confound the relationship with ETS exposure. Therefore, there is little evidence that important confounders were excluded. No association was seen with ETS exposure and prematurity in the regression analyses. The authors' interpretation that their data is indicative of an effect of ETS exposure during pregnancy, leading to growth retardation rather than preterm delivery, appears justified.

Ogawa et al. (1991)

Ogawa *et al.* (1991) examined ETS exposure in a study of almost 7,000 women who delivered a singleton in 1987 in Aichi Prefecture, Japan. Women were interviewed by medical staff before or soon after delivery. Each woman was asked about her smoking habits and those of her husband before and during pregnancy, as well as about the average length of ETS exposure per day during pregnancy at home, at work or elsewhere. Overall, about 15% of women smoked before pregnancy, but only 6% of women continued to smoke during pregnancy. Among all women, 62% reported some ETS exposure and 65% had husbands who smoked. Among women who had never smoked, there was a 24 gram decrement in mean weight of term births with exposure to ETS for two or more hours per day. Adjusting for a number of confounders yielded a weight decrement of 10.8 grams, which was noted as non-significant. The crude and adjusted odds ratio for LBW at term did not indicate any increased risk with ETS exposure (Table 3.3). Interestingly, the adjusted weight reduction associated with active smoking of 10

cigarettes per day was only 56 grams, compared to the 200 grams found in many other studies. The data on husbands' smoking status alone and pregnancy outcome were not presented.

Lazzaroni et al. (1990)

Lazzaroni *et al.* (1990) examined data from a multi-center, hospital-based study of about 1000 pregnant women in Italy. The analysis is based on questionnaires administered to women within 5 days of delivery of a newborn during 1989. Newborns born before 36 weeks and weighing less than 2000 grams were excluded, so prematurity and LBW could not be examined. ETS exposure was ascertained by asking the number of hours of exposure at home and work; anyone reporting a minimum of one hour per day was considered exposed (about 25% of the respondents fell into this category). Nonsmokers with ETS exposure were compared to those without, but both categories could include women that quit smoking during pregnancy. Almost 30% of women were considered active smokers during pregnancy. Mean birthweight of infants of women exposed to ETS was reduced 51 grams, which was not statistically significant. Adjusting for a number of important potential confounders by multiple regression indicated a weight decrement of 16.9 grams per hour of ETS exposure (p=0.07), or about 38 grams for any (versus no) exposure among nonsmoking women with term births (Table 3.3). Excluding women only exposed one hour per day yielded a greater decrement in weight of 61 grams (95% CI = -149.3 to 26.8), indicating that highly exposed women are at greater risk. The authors further noted that the mean birthweight of infants of women heavily exposed to ETS ($\geq$5 hours/day) was less than that of infants of light active smokers. The adjusted overall decrease in infant length was not significant (0.26 cm, 95% CI = -0.56 to 0.03).

Ahlborg and Bodin (1991)

Ahlborg and Bodin (1991) conducted a prospective study of 4,701 Swedish women reporting for prenatal care in 1980-83. They examined prematurity and LBW at term among nonsmoking women exposed to ETS, which was defined as living with a smoker during pregnancy or spending most of the time at work in rooms where other people were smoking. In an attempt to separate the effects of home and work exposure, the authors further limited the sample to working women. The adjusted odds ratio for term LBW and ETS exposure only in the home was 0.7 (95% CI = 0.21 - 2.3) and for prematurity was 0.5 (95% CI=0.23 - 1.1). These figures are based on very small numbers of affected births in the exposed group (n=3 and 7, respectively).

The manner in which the question to ascertain work exposure was asked would tend to identify a fairly heavily exposed group. The adjusted relative risk for workplace ETS exposure and prematurity was 1.3 (95% CI = 0.7 - 2.3) and for LBW at term was 1.1 (95% CI= 0.33 - 3.6) (Table 3.3). These women could also be exposed to ETS at home; further limiting the analysis to those with a nonsmoking partner increased these ORs (1.8 for prematurity and 1.2 for term LBW). The authors stratified the association (with any workplace exposure) by whether the work was full-time or part-time, in an attempt to examine a dose-response relationship. The adjusted relative risks among infants of full-time workers were increased somewhat for prematurity (RR=1.5, 95% CI= 0.87, 3.0) and

for term LBW (RR=1.4, 95% CI = 0.33 - 5.9). The authors also examined mean birthweight. Among these working women, home exposure was associated with a 34-gram decrement in mean birthweight, but workplace exposure was not associated with a birthweight reduction (Table 3.3). As noted earlier, these analyses must have been based on extremely small numbers.

This study offers a lot of data, but there are some difficulties with its analysis of fetal growth. First, the number of pregnancies included in each analysis was unclear. There were 4,701 pregnancies that were not excluded or lost to follow-up, but information was only available about the father's smoking for 4,075 (87%) of these. Further reductions were made to examine only nonsmoking women and working women, although the numbers presented in the tables do not appear consistent. In addition, it is not known if mean birthweight was determined in all livebirths or only in term births, as was the case for LBW. Secondly, the proportion of nonsmoking women living with a smoker seems low at about 15%, particularly because 37% of women overall reported smoking in the first trimester, calling into question the validity of the reporting of paternal smoking habits. With respect to the results, a weight reduction with ETS exposure at home, but not in the workplace seems inconsistent. On the other hand, ETS exposure among full-time workers may be slightly associated with term LBW. When the authors attempted to look at possible confounders to explain this (lifting, stress, etc.), they found little change in the association. The true association may be diluted in this study by the focus on only women highly exposed at work, so that those less exposed may fall into the comparison group. The authors did note an increased risk of prematurity and term LBW with maternal smoking.

Fortier et al. (1994)

A large study from Quebec, Canada also ascertained exposure at home and work (Fortier *et al.*, 1994). Women who had singleton livebirths in 1989 were interviewed by phone on average six weeks after delivery. Questions about ETS exposure included whether the subject resided with smokers and how much they smoked in her presence, as well as hours and intensity of exposure at work. Of the over 7,000 respondents, 4,644 nonsmokers were available for analysis, of which nearly half (49%) were exposed to ETS at home and/or work. The crude OR for any ETS exposure and IUGR was 1.3, but reduced to 1.1 (95% CI = 0.85 - 1.4) with adjustment for maternal weight, parity, previous LBW and caffeine intake (Table 3.3). ETS exposure at home only was not associated with IUGR (adjusted OR = 0.98), nor was there a dose-response trend. The risk of IUGR associated with workplace-only exposure was slightly greater (adjusted OR = 1.2) and showed evidence of a slight dose-response trend with heavier exposure, even when controlled for potential confounding by job characteristics. However, women exposed both at home and at work had IUGR rates more similar to the home-only exposed women (adjusted OR=0.94). Adjustment for previous LBW may be over-controlling, as such LBW may have been associated with ETS exposure as well. ETS exposure at any location was not associated with preterm birth. The authors noted that the odds ratios of IUGR in the nonsmokers most heavily exposed to ETS at work (1.30-1.36) were similar to those found in light smokers (1-5 cigarettes/day) in their study population.

Mainous and Hueston (1994)

Mainous and Hueston (1994) analysed data from the 1988 National Health Interview Survey (NHIS), a household interview conducted on a nationwide sample, examining pregnancies occurring in the past six years (mean was two years). ETS exposure was determined by asking respondents to categorize their contact with smokers (friends, co-workers or family members) as "occasional, often, always, or never" during pregnancy. There was little difference in the frequency of LBW infants among ETS exposed versus unexposed women. However, when examined by categories of increasing exposure, there was a trend towards increasing rates of LBW ($p < 0.01$). Controlling for race, parity, income and maternal age, the adjusted odds ratio was about 1.6 for the highest exposure category (Table 3.3) and was greater among non-whites (OR=2.3, 95% CI=1.1 - 5.0). Comparing mean birthweight, women in the highest exposure category had infants that weighed on average 84 grams less than unexposed infants (Table 3.3). No dose-response trend in mean birthweight was noted for lower levels, which the authors interpreted as evidence for a threshold effect. The weight decrements were unadjusted and information was not included about other potential confounders of the relationship with LBW. Further, this study may be subject to some recall error, as pregnancies could have occurred up to six years earlier and the measure of outcome (as well as exposure) was obtained from the women themselves. The qualitative measure of exposure used may be less subject to recall error than a more quantitative measure would have been. The main advantage of the study is its large, population-based sample.

Chen and Pettiti (1995)

Chen and Pettiti conducted a case-control study of IUGR among singleton, term infants born in 1991 in Contra Costa County, California. Controls were non-growth retarded, non-malformed infants identified from birth certificates. ETS exposure was ascertained by first asking about location (work, home, car, other) and then the total number of hours per week exposed to ETS for each trimester. The small sample of non-smokers is a major limitation of the study. In addition, a number of known risk factors for IUGR were not identifiable as such in this study, including infant gender, maternal weight gain and prenatal care, as well as alcohol use. By quintiles of average hours of exposure over all trimesters, there was no indication of an increased risk of term IUGR with greater exposure. Most women reported exposure in "other" places, but none of the locations considered showed evidence of increased risk of term IUGR. Adjusting for a variety of variables showed a decreased risk with exposure but very wide confidence intervals with home exposure or home and elsewhere (ORs about 0.5); work and car exposure had odds ratios around one. In addition to low power and a fairly high refusal rate, this study may be hampered by recall error, although subjects were interviewed fairly soon after delivery (mean was eight months).

Roquer et al. (1995)

Roquer *et al.* (1995) conducted a small study of Spanish women presenting for labor and interviewed them after delivery. ETS exposure was defined as "significant" if the woman was exposed to the smoke of 20 or more cigarettes per day at work or home; that is,

exposure to one smoker who smoked a pack or more per day or two smokers who each smoked a half-pack per day. A major problem with the design is that the interviewer measured the infant within four hours after birth, so outcome determination was not blinded with respect to exposure. The mean birthweight of infants whose mothers were exposed was 192 grams less than that of infants whose mothers were unexposed, and was comparable to the weight decrement in infants of women who smoked 1 to 9 cigarettes per day. Infants of mothers who smoked heavily had weight decrements of over 450 grams. No confounders were considered, but parity and employment status were similar in ETS-exposed and unexposed women. The rate of IUGR was about doubled with ETS exposure, again similar to that seen in infants of light smokers, but was not statistically significant (Table 3.3). ETS exposure was associated with a reduction of one centimeter in length ($p < 0.001$). This study is limited by its small size and lack of adjustment for confounders, as well as by the possible measurement bias (although weight is subject to less measurement error than length).

Rebagliato et al. (1995)

In the best of the new studies, Rebagliato *et al.* (1995) conducted a prospective cohort study (also in Spain) of non-smoking pregnant women. Subjects were interviewed in their third trimester of pregnancy and a saliva sample was collected for cotinine analysis. The investigators asked extensive questions about exposure from four sources and on different days of the week to calculate an average weekly exposure during pregnancy. Of the 710 nonsmoking women, 88% reported some exposure; their infants were on average 85 grams lighter than those of unexposed nonsmokers. However, no dose-response trend was evident and results were not consistent by source, with exposure at home not resulting in a birthweight decrement. In a multiple regression model which adjusted for a number of covariates including gestational age (but not alcohol use), the highest exposure category was associated with a 41 gram decrement in birthweight (Table 3.3), while other categories had decrements ranging from 26 to 77 grams. Because of the small numbers of subjects in these categories, none of the weight decrements were statistically significant. More women were exposed at home, and for longer periods of time, so the inconsistent results are difficult to explain. However, exposures at work may be more intense, with more smokers present.

3.2.2.4 Fetal Growth and Biomarkers of ETS

There has been an effort in the past 10-15 years to validate tobacco smoke exposures using biomarkers, and a few studies have examined biomarkers in relation to pregnancy outcome in that time, with two additional studies published in 1995 (Table 3.4). Cotinine is the preferred biomarker because of its specificity to tobacco smoke exposure and longer half-life (20-30 hours in plasma) than nicotine (see chapter on *Exposure Measurements and Prevalence*). Nevertheless, cotinine only reflects relatively recent exposures and there is much inter-individual variation in its metabolism. Thiocyanate, a detoxification product of cyanide, has a longer half-life than cotinine (3-14 days) but is not as specific to tobacco smoke.

Hauth et al. (1984)

Hauth *et al.* (1984) looked at thiocyanate concentrations as a biomarker of ETS exposure in 163 women who had had a term pregnancy, by drawing maternal serum at the time of admission to labor and delivery. Thiocyanate (SCN) levels were compared among three groups, defined as smokers (10-40 cigarettes/day), passive smokers (live or work with a smoker), and nonsmokers. Umbilical cord blood was obtained immediately after birth. Maternal and cord blood SCN levels were significantly greater in smokers than in the other two groups, but the levels in passive smokers were only slightly greater than those in nonsmokers. There was a significant inverse relationship between umbilical cord SCN level and birthweight in infants born to smokers (published $r = 0.74$, $p<0.001$), but not in infants of passive or nonsmokers. The authors reported that infants of passive smokers had similar birthweights as those of nonsmokers, but the data were not presented. No confounders were assessed in this analysis. Another problem is that blood obtained at the time of labor may not accurately reflect exposure earlier in pregnancy, particularly if a woman exposed to ETS at work has left her job near the end of pregnancy.

Haddow et al. (1988)

In the largest biomarker study to date, Haddow *et al.* (1988) analyzed blood sampled during the second trimester of 1,231 pregnancies of nonsmoking white women in Maine. The authors defined ETS exposure as a cotinine level between 1.1 and 9.9 ng/ml, with lower levels split into two groups: those less than 0.5 ng/ml, which was the lower limit of detection; and 0.5-1.0 ng/ml. Women who had levels of 10 ng/ml or greater (n=29) were excluded. The authors found a crude decrement of weight between the highest and lowest groups of 107 grams, or 108 grams ($p<0.001$) after adjustment for a number of important confounders. Compared to the group with cotinine levels 0.5-1.0 ng/ml, the ETS-exposed group had an adjusted weight decrement of 104 grams (95% CI= -173 to -35) (Table 3.4). The authors also examined cotinine level as a continuous variable and found a weight decrement of 28 grams per ng/ml of cotinine ($p=0.04$). The mean level of cotinine was 2.14 ng/ml in the ETS-exposed group, which would predict about a 60-gram deficit overall. This, combined with data on active smoking, led the authors to suggest that the relationship of cotinine to birthweight may not be linear. However, this discrepancy may also be due to inter-individual variations in cotinine metabolism. The authors also mentioned that LBW was increased 29% in the ETS-exposed group, but no further data were provided.

Overall, this appears to be a well-conducted study. While the authors reported that in their previous work cotinine levels correlated well with self-reported exposure, data on self-reported ETS exposures unfortunately were not available for comparison to the cotinine levels. Because data were obtained from birth certificates, one variable not included in the analysis was alcohol consumption. However, nonsmokers are unlikely to be heavy drinkers, or enough so to explain the observed results. Another variable not mentioned was gestational age, a strong predictor of weight, so it is not possible to determine whether the weight decrement seen is due to prematurity or growth retardation.

Ueda et al. (1989)

A study from Japan (Ueda *et al.*, 1989) reported finding an association of ETS exposure (as well as active smoking) with lowered birthweight, based on an analysis of cotinine levels. Women attending prenatal clinics (n=257) were interviewed and samples of blood and urine were obtained. The authors classified women into seven categories of exposure based on their self-reported active smoking and exposure to ETS at home and elsewhere. Of the nonsmokers, most (84%) reported some ETS exposure. Cotinine levels in maternal urine appeared to differentiate those exposed to ETS from those not exposed. Mean cotinine levels were lowest in women who reported no exposure (3.98 ± 3.2 ng/ml), intermediate in women who reported exposure only at home (10.9 ± 39 ng/ml) or only outside the home (11.1 ± 20 ng/ml), and highest among those exposed in both places (55.5 ± 135 ng/ml). For comparison, the mean in active smokers was 228.4 ± 214.6 ng/ml. Cotinine levels in maternal serum were not well correlated with self-reported exposure.

Despite the relatively high urinary cotinine levels in exposed nonsmokers, relative birthweight did not appear to vary by self-reported ETS exposure category. Relative birthweight (RBW) was calculated by comparing the true birthweight to a national standard, by gestational age. The investigators plotted cotinine levels by RBW and found a "correlation/relation" that was significant by the chi-square test ($p<0.01$). However, this is an unconventional statistical method for examining a correlation and neither the magnitude of the correlation nor the slope of a regression line was provided. The authors compared the RBW in two groups of women defined by whether their urinary cotinine levels were above or below 9 ng/ml, which represented the mean ±1.5 standard deviations of the unexposed group's level. The RBW of infants of women with higher cotinine levels (n = 46) was lower (96.2 ± 12.9%) than that of infants of women with lower cotinine levels (n=127) (102.4 ± 10.1%; $p <0.001$). However, it is not clear whether active smokers were excluded. Although active smokers represent only a small proportion (6.6%) of the total group, they may account for a fairly large proportion of those with elevated cotinine levels. The results of this study are difficult to evaluate due to insufficient information and unusual methods. The lack of consistency between cotinine levels in maternal urine versus serum is difficult to explain.

Mathai et al. (1990)

In one of the studies of Mathai *et al.* (1990) previously mentioned, the investigators obtained maternal urine to measure cotinine levels at 16 and 32 weeks of pregnancy, and at delivery. Data from 285 women were included, of which about 47% were nonsmokers, 19% were nonsmokers who lived with a smoker, and 34% were active smokers at study entry. Cotinine levels increased across the exposure groups, as well as slightly with increasing gestational age, although whether these differences were statistically significant was not specified. Infant birthweight was regressed against a number of co-covariates, with exposure in one model included as both the number of cigarettes smoked actively and exposed to passively at 16 weeks, as well as a separate model with cotinine levels replacing self-reported exposure. Alcohol was not included as one of the variables. There was a 25 gram decrease in birthweight with every μg cotinine/mg creatinine (creatinine is

used as a measure of the concentration of the urine). The mean cotinine level of passive smokers was 0.85 μg/mg creatinine; hence only a very small weight decrement would be predicted, rather than the 66 gram decrement observed. This measure also underestimated the decrement seen with active smoking, again indicating a non-linear effect. Cotinine levels explained slightly more of the variation in birthweight than did self-reported tobacco exposure. This study would have been more valuable for assessing an association of ETS exposure (as measured by cotinine) and birthweight if smokers were excluded, particularly if there is a non-linear relationship. The fact that cotinine was detected in the urine of some of the nonsmokers who did not report living with a smoker (mean = 0.29 μg/mg creatinine) indicates that some of them are probably exposed to ETS. This confirms the problem inherent in studies that base ETS exposure status only on reported household exposure. If this misclassification of exposure is non-differential, it tends to bias effect estimates toward the null.

Eskenazi et al. (1995)

Eskenazi *et al.* (1995) used data from the Child Health and Development Studies in California (as did Yerulshalmy, 1971) to look at birthweight in relation to cotinine measured in stored serum samples. An interview was conducted and sera collected around the 27-28th week of pregnancies that occurred between 1964 and 1967. The infants of women who had never smoked during pregnancy experienced an average weight decrement of 45 grams (Table 3.4). This figure was similar unadjusted or in a multiple regression model that included a number of covariates including gestational age, as well as women who were smokers. The authors reported that alcohol and caffeine consumption were considered, but did not improve the model. The crude mean birthweight of ETS-exposed infants was similar to that of infants of light smokers, but there was a 30 gram difference after adjustment. The highest cotinine level (>165 ng/ml, e.g. active smoking) was associated with a 230 gram weight decrement. Examining cotinine as a continuous variable (including smokers), there was a 1 gram weight decrement for each nanogram per milliliter increase in cotinine. This is based on a linear model, which may not be appropriate. The authors also found a slight increase in LBW associated with ETS exposure (Table 3.4), but no effect on gestational age or prematurity (unadjusted).

The definition of ETS exposure in this population may be problematic, as the reported exposure rate of only 5% is so low, especially for the 1960's. Of those considered unexposed based on cotinine level, 50% reported having a spouse who smoked, so the reference group may have included exposed women who were not identified by the relatively high detection limit (2 ng/ml). Of reported nonsmokers with detectable cotinine levels, one-third had levels greater than 10, and were excluded. These may in fact have been nonsmokers who were more highly exposed, as there would have been fewer reasons to misreport smoking status in that time period (as the authors themselves suggest). Use of current cotinine levels to define ETS exposure (versus active smoking) may not be appropriate for these older samples and an assay that was apparently less sensitive. Another problem with exposure assessment in this study may have been the age (25 years old) of the samples.

Rebagliato et al. (1995)

As noted in Section 3.2.2.2, Rebagliato *et al.* (1995) studied ETS exposure in 710 nonsmoking women using a questionnaire and sampling saliva for cotinine. The investigators examined birthweight by quintiles of cotinine levels less than 14 ng/ml, with subjects having cotinine levels of 0 to 0.5 ng/ml serving as the reference group. In the highest quintile (>1.7 ng/ml), there was a crude weight decrement of 98 grams, which was reduced slightly to 87 grams after adjustment for covariates (Table 3.4). There was little evidence for a dose-response trend, but the highest category examined does not represent a particularly high ETS exposure level. For comparison to Haddow *et al.* (1988), the weight decrement associated with any cotinine level greater than 0.5 ng/ml was 35 grams. The adjusted weight decrement found with high cotinine level was greater than that found with high self-reported exposure. However, in a separate analysis of exposure measures (Rebagliato *et al.*, 1995b), the authors reported that duration of recent exposure to each source of ETS (as self-reported) and the summary measure at all locations were significantly correlated with cotinine levels (Spearman's $r = 0.52$ for all locations). The apparent inconsistency may be due to differences in the way women report their own exposure, so that some misclassification results.

3.2.3 Animal Studies of Fetal Growth and Tobacco Smoke Exposure

A number of studies of the effects of tobacco smoke on intrauterine growth in rodents have been reported in the literature. The majority of available studies attempted to simulate active smoking by using mainstream smoke (MS), and some delivered the smoke in bursts or "puffs". Of ten such studies reviewed (see Table 3.7), five reported significant group differences in intrauterine growth retardation ranging from 4 to 31% relative to controls. In two other studies, pup weights were lower (6-16%) in the groups exposed to tobacco smoke, but group differences were not significant. Pup weights were determined at the end of gestation after removal of pups by hysterotomy, or after spontaneous birth. The phrase "fetal weight at term" rather than "birthweight" is used to describe the results of the animal studies. Premature delivery is rare in laboratory rodents, so that weight for gestational age is not an issue.

In addition to these studies of mainstream smoke, three recent studies in rats (Table 3.7) which used exposures characterized as "sidestream smoke" (SS) are described below.

Leichter (1989)

Leichter (1989) used a two-hour daily exposure throughout pregnancy and found a statistically significant 9% reduction in mean fetal weight at term relative to controls. Fetal weights in the SS-exposed group were also significantly smaller than in a pair-fed group which was included to control for effects of sidestream smoke on food intake. The smoke was not characterized chemically in this study.

Witschi et al. (1994)

Witschi *et al.* (1994) used a six-hour exposure on days 3-10 of gestation and found identical fetal weights at term in the SS-exposed group and in controls. However, litter

size was significantly lower in the sidestream smoke group. Reduced litter size can sometimes be viewed as offsetting an effect on intrauterine growth, due to a greater availability of nutrients for each fetus when there are fewer fetuses per litter (Romero *et al.*, 1992). Also, exposures in this study did not extend into the fetal period of gestation when weight gain is most rapid.

Rajini et al. (1994)

Rajini *et al.* (1994), from the same research group as Witschi *et al.* (1994), used exposures on days 3, 6-10, and 13-17 of gestation and found a statistically significant 7% reduction in mean fetal weight at term in the SS-exposed group relative to controls. In this study there was no sidestream smoke effect on litter size; further, the exposure period extended into the fetal period of gestation. There were no group differences in maternal weight gain during pregnancy in this study.

3.2.4 Discussion and Conclusions

More than twenty-five epidemiologic studies of the relationship between fetal growth and ETS exposure have been reviewed. All but one of the studies that examined mean birthweight have shown a decrement with ETS exposure, although some of the weight differences were small (Figure 3-1). Only a few studies examined fetal length, and though results were in the direction of a small decrement with ETS exposure (0.25-1.1 cm), two were unadjusted, so conclusions cannot be reached. Fifteen studies have examined low birthweight or “small for gestational age” as shown in Figure 3-2. The figure indicates that the majority of studies which have examined these outcomes have shown a slightly elevated risk with ETS exposure. The area of overlap of the confidence intervals is consistent with up to a 1.4- or 1.5-fold increased risk of small fetal size; however, it is also consistent with there being no association. Only a few of the findings were statistically significant on their own. Taken together, however, they support a slight increase in LBW or IUGR in association with ETS exposure. There was little evidence found for an association with preterm birth.

The biomarker studies, in particular Haddow *et al.*'s study (1988), provide the most convincing evidence of an effect on growth (or weight). The Haddow *et al.* study is based on measurement of biomarkers, addressing exposure assessment issues; it has adequate control of confounders; and it has a large study population. As such, the findings of a 100 gram weight deficit must be considered strong evidence, but in need of replication. The biomarker data of Ueda *et al.* (1989) and Mathai *et al.* (1990) add some supportive evidence, but are not comparable to the Haddow study because analyses were not limited to nonsmokers. The weight decrement found by Haddow *et al.* is about half the magnitude of that seen with active smoking and is thus greater than might be expected based on cotinine levels measured in those exposed to ETS compared to active smokers. Nevertheless, this magnitude of effect relative to that of active smoking was reported in a number of other studies based on self reported ETS exposure (Borlee *et al.*, 1978; Rubin *et al.*, 1986; Schwartz-Bickenbach *et al.*, 1987; Campbell *et al.*, 1988; Martin and Bracken, 1986; Lazzaroni *et al.*, 1990). Furthermore, the Haddow *et al.* (1988) data suggest that the association with birthweight is not linear with "dose" as measured by

cotinine level. The two newer biomarker studies confirm Haddow *et al.*'s results but found lower weight differences. In Eskenaz *et al.*'s (1995) study, only a small proportion of the study subjects were found to be exposed, as defined by cotinine level, and this lack of exposure did not correspond with self-reporting; these results raise the possibility of misclassification and the dilution of an effect. Rebagliato *et al.* (1995), like Haddow *et al.* (1988), found a statistically significant effect for any ETS exposure and a similar magnitude (88-105g) of birthweight decrements with higher exposures (defined by cotinine level).

The second strongest evidence comes from studies that attempted to ascertain total ETS exposure from multiple sources, with adequate control of confounding. The four such studies published before 1994 (Table 3.3) showed small decrements in mean birthweight after adjustment (20-40 grams). Three (and perhaps four) of these studies examined term births only; weight differences in this group would be less variable than in all births, and are thus not comparable to the majority of studies. In addition, the studies were not comparable in their definition of exposure, and some of the risk measures may be diluted by inclusion of less-exposed pregnancies in the reference groups, particularly in Ogawa *et al.* (1991) and Ahlborg and Bodin (1991). The studies published in 1994 and 1995 (Table 3.3) found more variable weight differences, but some of the measures presented were unadjusted or in the highest exposure subgroup only, and thus are not entirely comparable to the earlier studies' results. Two of the studies indicated that more highly exposed women may be more greatly affected (Lazzaroni *et al.*, 1990; Mainous and Hueston, 1994). However, Rebagliato *et al.* (1995) did not find a consistent dose-response trend with self-reported exposure; this was due in part to a finding of no effect with home exposure, only with exposure outside the home, in this Spanish study. Based on these studies an average weight decrement of 25-50 grams appears plausible, and is closer to what might be expected based on relative cotinine levels in those exposed to ETS versus active smokers.

Among the studies which ascertained ETS exposure from multiple sources, only one found a strong association with growth retardation (Martin and Bracken, 1986). The Martin and Bracken study has been criticized (Hood, 1990) because of its low rate (2%) of LBW. However, the rate of LBW at term is expected to be much less than overall rates of LBW: Ogawa *et al.* (1991) found a rate of 3% and Ahlborg and Bodin (1991) observed a rate of only 1.5%. Two of the newer studies also found similarly elevated risks, although one was unadjusted and based on small numbers (Roquer *et al.*, 1995), and the other found an increased risk only with high exposure (Mainous and Hueston, 1994) (Table 3.3). Two studies (Ahborg and Bodin, 1991; Fortier *et al.*, 1994) found greater associations with workplace than home exposures, which further increased with greater number of hours worked. The case-control study by Chen and Pettiti (1995) also found some differences between work and home exposure, with no effect at work but a slightly protective effect at home. However, in each these three studies which examined home and work exposure separately, the confidence intervals were wide and overlapped, so the effects of exposure at home and at work may not be trully different. Some studies have found that subjects were more likely to be exposed at work than at home (Fortier *et al.*, 1994), or that they were exposed longer at work than at home (Lazzaroni *et al.* 1990);

however, this may vary by culture, as Ogawa *et al.*(1991) found more women were exposed at home. Workplace exposure may also differ from that at home due to the number of smokers contributing to the ETS and the influence of environmental conditions (*e.g.*, air exchange rates, temperature).

Overall, the weight differences observed in the studies based on exposure to spousal or household smokers vary greatly, from a decrement of three to over 200 grams (Table 3.1 and Figure 3.1). The studies are difficult to compare because of their many differences, including: when they were conducted (over a 25-year timespan); the location and nationality of study populations; the range of sample size and sample selection; the extent to which confounders were controlled; and the analytic methods used. Furthermore, the crude assessment of exposure in most studies allows for a great variation in the actual "amount" of exposure being compared. The two studies with the highest birthweight decrements provided only crude estimates, unadjusted for potential confounders, and neither included population-based samples.

Of these studies of mean birthweight and exposure to household smokers, the highest quality studies--based on study design, sample size and control of confounders (Brooke *et al.*, 1989, Chen *et al.*, 1989, Rubin *et al.*, 1986; Campbell *et al.*, 1988; Mathai *et al.*, 1992; Zhang and Ratcliffe, 1993)--found weight decrements ranging from 15 to 100 grams. Martinez *et al.* (1994), the only one of the new studies in this category, found a statistically significant adjusted weight difference in the same range. Two of these studies (Campbell *et al.*, 1988; Rubin *et al.*, 1986) did not exclude active maternal smokers, but rather adjusted for them. Four of these studies reported examining the data for a dose-response relationship; such a relationship was observed by Rubin *et al.* (1986) and Martinez *et al.* (1994), while the two studies from Shanghai reported no or an inconsistent trend (Chen *et al.* 1989; Zhang and Ratcliffe, 1993). In addition to these studies, the Saito (1991) study, which was the largest but did not control for confounders, also found a mean weight decrement in the same range, and demonstrated a dose-response relationship. These studies provide further evidence for a decrement in birthweight associated with ETS exposure.

The studies based on paternal or household ETS exposure tended to show slight (or no) increases in the risk of LBW or IUGR. The best, and the most recent studies (conducted in the past decade, see Table 3.2), were all from Asia and reported ORs ranging from 1.1 to 1.7. Two of these showed no indication of a dose-response trend (Chen *et al.*, 1989; Zhang and Ratcliff, 1993), whereas two others showed some evidence of a trend (Nakamura *et al.*, 1988; Saito, 1991).

In general, the results of animal studies support an effect of sidestream smoke exposure during pregnancy on intrauterine growth. In particular, the recent study by Rajini *et al.* (1994) demonstrated an effect on intrauterine growth in the absence of an effect on maternal weight gain in a situation using well-characterized sidestream smoke exposures. The extent of growth retardation in the animals studied was greater than that reported in infants of ETS-exposed women, but the exposure levels were also higher (*e.g.*,

concentrations of total suspended particulates were about 10 times higher than the average exposure caused by indoor cigarette smoking).

Although it is difficult to separate out the possibility of uncontrolled confounding or misclassification in an individual study with a relative risk of 1.2-1.4, the consistency of the association found in these studies from different countries strengthens the evidence for causality, as do the corresponding effects seen in animal studies. Furthermore, there is some evidence that higher exposures may have effects approaching those expected in light smokers. Additional studies might help clarify any differences between chronic low level exposure and shorter higher exposures.

Lending further support in terms of a biological basis for these findings from epidemiologic and animal studies are the well-established relationships, first, between active smoking and fetal growth retardation in humans, and second, between constituents of tobacco smoke (e.g., nicotine, carbon monoxide, toluene, cadmium) and fetal growth retardation in animals. There appears to be sufficient evidence that ETS is associated with a decrement in birthweight (and fetal growth retardation), based on all sources of data with primary emphasis on the high quality epidemiologic studies. The effect is of a small magnitude (perhaps 25-50 grams) that may not be clinically significant for an individual infant at low risk. Yet, if the entire birthweight distribution is shifted lower with ETS exposure, as it appears to be with active smoking, infants who are already compromised may be pushed into even higher risk categories. Low birthweight is associated with many well-recognized problems for infants and with perinatal mortality. A meta-analysis of studies conducted up to mid-1994 reported a weighted average of a 28 gram decrement in mean birthweight (95% CI= -40 to -16), a summary odds ratio of 1.2 (95% CI= 1.1 1.3) for IUGR or LBW at term and 1.4 (95% CI=1.1 1.8) for LBW (Windham *et al.*, 1995a). An increased risk of 20-40% in LBW with ETS exposure would affect a large number of infants in California. Assuming relative risk estimates of 1.2 to 1.4, a rough estimate of the number the ETS-related low birthweight newborns in California is 1,200 to 2,200.

3.2.4.1 Risk Attributable to ETS Exposure

Low birthweight affects 6-7% of the births in the United States (U.S. DHHS, 1996) and thus, of the 551,226 births in California in 1995 (California Department of Finance, 1996) approximately 36,000 may have been of low birthweight. Both active smoking and ETS exposure are risk factors for low birthweight, and estimates of attributable cases due to ETS exposure are more accurate when active smoking prevalence is taken into account. From the equations used by U.S. EPA (1992) for estimating attributable lung cancer risks, attributable risk (*a*) for low birthweight due to ETS exposure can be estimated by

$$a = (1 - P_S)P_E(R_E - 1) / [(1-P_S)P_E(R_E - 1) + P_S(R_S(P_E R_E + 1 - P_E)) + 1]$$

where P_S is the prevalence of smokers in the population, P_E the prevalence of ETS-exposed nonsmokers, R_S the relative risk of low birthweight in smokers relative to nonsmokers, and R_E the relative risk of low birthweight in ETS exposed nonsmokers relative to non-ETS-exposed nonsmokers. The above expression assumes that there is no

tobacco-related impact on birthweight among those characterized as nonexposed. In the event that this is incorrect, the expression above is biased in the direction of underestimating ETS-related attributable risk.

The prevalence of exposure can be estimated from the results of the 1993 California Tobacco Survey reported by Pierce *et al.* (1994; 1996, personal communication): 9.4% of women who are pregnant are active smokers; 21.2% of pregnant nonsmokers are exposed to ETS, based on the proportion of 18-44 year old nonsmoking women exposed at home or work. This may understate the prevalence of ETS exposure of pregnant women because those exposed in other indoor locations have not been included. To estimate the relative risk of low birthweight due to active smoking and ETS exposure, we use ORs (which we take to be approximations of the relative risk) of 2 and 1.2 to 1.4, respectively. Applying these values to the equation given above, the proportion of all low birthweight newborns in California that may be associated with ETS exposure is estimated to be 3.3 to 6.2%. This corresponds to 1,200 to 2,200 newborns in California in 1995 with low birthweight associated with ETS exposure.

3.3 Spontaneous Abortion and Perinatal Mortality

In this section, studies evaluating the effect of ETS on spontaneous abortion and perinatal mortality are described. For the purposes of this discussion, perinatal mortality is defined as death in the period from 20 weeks gestation to 28 days post-delivery. Perinatal mortality includes stillbirths (fetal death from 20 weeks to term) and neonatal deaths (death between birth and 28 days of life). Relatively few studies have assessed the effect of ETS exposure on perinatal mortality. Spontaneous abortion or miscarriage is currently defined as pregnancy loss in the first 20 weeks of gestation, but was defined as loss up to 28 weeks in older reports. Some authors have combined spontaneous abortions with stillbirths to look at prenatal and perinatal deaths.

Perinatal death encompasses a wide variety of causes or diagnoses (*e.g.*, *abruptio placenta*, premature rupture of membranes (PROM), severe malformation) which may result from different etiologic factors. Identification of confounders is particularly complex. As prematurity and LBW are risk factors for neonatal death, birthweight and gestational age should be considered when studying perinatal mortality. When examining spontaneous abortion, maternal age, prior history of pregnancy loss and socioeconomic status indicators at a minimum should be considered as potential confounders.

3.3.1 Overview of Human Studies of Spontaneous Abortion and Perinatal Mortality and Maternal Smoking During Pregnancy

The literature on the association of active maternal smoking during pregnancy and fetal loss is not as definitive as it is for birthweight. Many studies have found an association with perinatal mortality (see Stillman *et al.*, 1986; Kleinman *et al.*, 1988). The 1980 report of the Surgeon General states that the risk of mortality "increases directly with increasing levels of smoking during pregnancy", and that the effect is greater in women with other risk factors (U.S. DHHS, 1980). Furthermore, the increased risk appears to be related to problems of pregnancy and prematurity, rather than to abnormalities of the

neonate. Some of the perinatal mortality has been found to have resulted from placenta praevia, in which the placenta separates from the uterine wall. This is consistent with the changes associated with exposure to carbon monoxide and nicotine described earlier in Section 3.2.1.

Active maternal smoking is often cited as a risk factor for spontaneous abortion in descriptive overviews (Stillman *et al.*, 1986; Pirani, 1978; Kline and Stein, 1984), but the data are not consistent. Studies which reported an association found odds or rate ratios of 1.5-2.0, particularly with heavier smoking (Kline *et al.*, 1977). Not all of these studies adjusted for confounders, such as alcohol consumption. Several studies, including some discussed below (Windham *et al.*, 1992; Hemminki *et al.*, 1983), did not find substantial associations. Inconsistencies may be due to the fact that the study populations were from different backgrounds in different time periods, in which the pattern of active smoking during pregnancy may have varied. As smoking during pregnancy becomes less prevalent, fewer women are exposed and an association becomes more difficult to detect. If there is an association of perinatal mortality with active smoking, it appears more likely to occur with later fetal losses (U.S. DHHS, 1980; Kallen, 1988).

3.3.2 Human Studies of Spontaneous Abortion and Perinatal Mortality and ETS Exposure

Eight studies were reviewed. Two recent studies suggest a link between ETS and spontaneous abortion, but a third does not. Several earlier studies also suggested an increased risk of neonatal death associated with paternal smoking. Studies of stillbirth did not suggest increased risk.

Comstock and Lundin (1967)

In an early study (Table 3.5), Comstock and Lundin (1967) examined stillbirth and neonatal death rates in relation to parental smoking. The sample consisted of 376 live births born in Maryland between June 1953 and 1963, and 476 stillbirths or neonatal deaths in the same time period. Smoking status was determined from a special population census conducted in the study area, and could not be specifically related to the pregnancy under study. The authors reported "no significant differences" in the rates of stillbirth by paternal smoking status, but no data were shown. Neonatal death rates, adjusted for infant gender and paternal education, were elevated in infants with nonsmoking mothers and smoking fathers (17.2 per 1000) compared to infants with no parental smokers (11.9 per 1000). Neonatal death rates were highest when both parents smoked (26.5 per 1000). There was no statistical testing of the differences in the adjusted rates. Because the adjusted rates were very similar to the crude rates, we calculated a crude odds ratio and 95% confidence interval for the association of neonatal death and paternal smoking (OR=1.45, 95% CI= 0.9 - 2.4). The authors noted that neonatal mortality rates were also increased among a small group of infants whose mothers did not start smoking until after pregnancy. This could reflect ETS exposure of the infant. Only a few confounding factors were addressed in this study, and the possibility that birthweight could be the mediating factor in neonatal mortality was not considered.

Tokuhata (1968)

Tokuhata (1968) used data from a case-control study of reproductive cancers in Tennessee to examine infertility and fetal losses in relation to the smoking experience of the couples. The results showed that husbands' smoking status was unrelated to fetal loss (RR=1.1). This study is limited in several ways. First, information about miscarriage and stillbirth was obtained from a next of kin long after the events in question had occurred. This makes the ascertainment of miscarriage particularly unreliable. Second, the entire reproductive period was included: some subjects had had multiple pregnancies and the observed events were not independent. Third, lifetime smoking history was used, which may not pertain to specific pregnancies. Information on amount smoked or potential confounders was not addressed.

Yerushalmy (1971)

Yerushalmy's (1971) analysis of data from the comprehensive Child Health and Development Studies conducted in 1960-67 included an examination of neonatal mortality rates among low birthweight infants only, a select group. He found higher mortality rates among LBW births to couples in which the father was a smoker, particularly among blacks. The data presented in a figure in the study report indicate about a 10% increase in the rates among whites and a 35% increase among blacks. This pattern was seen whether the mother was a smoker or not. No raw data were presented for estimating an effect measure or confidence interval, nor were confounding variables considered.

Mau and Netter (1974)

In their report of a large prospective study in Germany (see Section 3.2.2.1), Mau and Netter (1974) examined the association of paternal smoking with perinatal mortality (the definition of which was not stated). The authors found an increased rate of perinatal mortality among pregnancies where the father smoked 10 or more cigarettes per day, both for all women and for nonsmoking women ($p<0.01$). There was not a monotonic dose-response relationship with the amount the husband smoked (there was a slightly lower mortality rate for infants of lighter paternal smokers (1-10 cigarettes per day) than for infants of nonsmokers). Calculating a crude rate ratio for the heavier smoking category yields an approximate measure of 1.5 ($p < 0.05$) (Table 3.5). Stillbirth rates were identified separately, and were also included in the perinatal mortality rates. Stillbirth rates increased only slightly with heavier paternal smoking among infants of all women (RR=1.2), with no further information provided on nonsmoking women. Mau and Netter (1974) noted that the rate of miscarriage in women whose husbands smoked more than 10 cigarettes per day was slightly higher than among those whose husbands did not smoke (9.3% versus 8.2%). This difference was not statistically significant and no further data were presented.

The small (or lack of) association of paternal smoking with either stillbirth or miscarriage indicates that the association with perinatal mortality may be due to increased neonatal mortality. The authors examined various confounding factors and judged that they had little effect on the association of paternal smoking and perinatal mortality, but they were

not adjusted for simultaneously. The authors apparently did not adjust for birthweight because they did not find a significant association of low birthweight with paternal smoking in their study. They did exclude births with congenital malformations, and found that the increase in perinatal mortality persisted.

Koo et al. (1988)

In a small study of nonsmoking female controls (n=136) from a lung cancer study in Hong Kong, Koo *et al.* (1988) compared life-history variables by the husband's smoking status. The authors reported that women whose husbands had ever smoked were 40% more likely to have had a miscarriage or abortion, and twice as likely to have had a dilation and curettage (D & C) than wives of nonsmokers. The results were statistically significant ($p < 0.03$) for D & C only, and the authors claimed that most of those pregnancy losses would have been spontaneous rather than induced abortions, but that was not substantiated. Wives of smokers also tended to have more pregnancies, which was not accounted for in comparing the percent of women (versus pregnancies) with one or more pregnancy losses, nor were potential confounding factors considered.

Lindbohm et al. (1991)

A case-control study from Finland, designed to examine the effect of paternal lead exposure on spontaneous abortion, also reported paternal smoking habits (Lindbohm *et al.*, 1991). The crude odds ratio for spontaneous abortion associated with any paternal smoking was 1.3 (95% CI = 0.9 - 1.9) (Table 3.5). Maternal smoking had an OR of 1.5 (95% CI= 0.9 - 2.4), but was not taken into account in the association with paternal smoking. This study may not be generalizable because it targeted men who had been identified through a blood lead monitoring service.

Ahlborg and Bodin (1991)

The previously described study of Ahlborg and Bodin (1991) had information about ETS exposure at home as well as in the workplace, ascertained in a prospective study of about 4700 pregnancies in Sweden. ETS exposure (any versus none) was not found to be associated with excess risk for hospital-ascertained intrauterine deaths (spontaneous abortions plus stillbirths) among nonsmoking mothers. However, there was an excess risk among working women with workplace exposure, with an adjusted rate ratio of 1.5 (95% CI= 0.98 - 2.4) (Table 3.5). This risk did not vary much by whether the woman worked full- or part-time, or whether or not her partner smoked. When a distinction was made on the basis of whether the loss was early (≤ 12 weeks) or later in pregnancy, the association with workplace exposure appeared limited to early losses (RR=2.2, 95% CI=1.2 - 3.8) rather than later losses (RR=1.1). Among working women, exposure only in the home was not associated with intrauterine death.

This study has several strengths, including its ascertainment of multiple sources of exposure, its use of adequate numbers of pregnancies for assessing fetal loss and its thorough control of known confounders. However, the fetal loss rate was low and first trimester losses before prenatal care began were probably under-ascertained. Several of the findings were somewhat inconsistent, such as an association only with workplace

exposure and not home exposure. The question format, however, would tend to yield a more highly exposed group at work than at home (*e.g.* "Do you spend *most* of your time at work in rooms where other people are smoking?" versus "Do you live with a person who smokes inside your home?"). It might have been helpful if the authors had examined the hours of exposure at home or the amount smoked by the household smoker. Secondly, the association of ETS exposure at work with intrauterine deaths in this study is on the same order or greater than the association found for active smoking and intrauterine death. Lastly, in contrast to the ETS findings, the association with active smoking is more striking in later rather than early pregnancy losses.

Windham et al. (1992)

Windham *et al.* (1992) examined ETS exposure in a large case-control study of spontaneous abortion conducted in California. Cases, which were confirmed by medical records, were compared to live born controls frequency matched (to cases) by hospital and date of mother's last menstrual period. The ascertainment of exposure included a question on the amount smoked by the "father of the pregnancy", as well as a separate question on whether the subject was regularly exposed to cigarette smoke for an hour or more per day during the first 20 weeks of her pregnancy. The adjusted odds ratio for self-reported ETS exposure of one hour or more per day among nonsmokers was 1.6 (95% CI= 1.2 - 2.1), with a somewhat greater association among second trimester than first trimester losses (Table 3.5). The association varied little with the woman's employment status. For amount smoked by the father, the adjusted odds ratios were all close to unity. However, among women reporting ETS exposure, the association was slightly greater if her partner smoked (OR=2.0) than if he did not (OR=1.5), potentially indicating heavier ETS exposure.

This study lends some support to the findings of Ahlborg and Bodin (1991) of an increased risk of fetal death associated with ETS exposure. Of further note is that the Windham *et al.* (1992) study also found a lower association of spontaneous abortion with active smoking than with ETS exposure, even when active smokers were compared to nonsmokers with no ETS exposure (OR = 1.3). An inconsistency is that Windham *et al.* (1992) found a slightly greater association with later abortions, while Ahlborg and Bodin (1991) found a greater association with earlier spontaneous abortions. However, in the Swedish study the late pregnancy losses also included stillbirths. Recall bias may be a concern with a retrospective study, although the questions about ETS exposure were embedded in a series of questions about other exposures and were not the main hypothesis of the Windham *et al.* study.

Windham et al. (1995b)

In a recently reported prospective study (Windham et al. (1995b), unpublished symposium presentation), the finding of an association between ETS exposure and spontaneous abortion was not confirmed. In that study, pregnant women were interviewed in the first trimester regarding the number of hours per day of ETS exposure at home or work, from which a daily total for each woman was calculated. Among the more than 4000 non-smokers in the study, there was no association with any measure of ETS exposure,

including paternal smoking, nor was there any dose-response relationship (adjusted OR for any ETS = 1.0, 95% CI = 0.80 - 1.3). However, among women who consumed moderate amounts of alcohol (greater than or equal to three drinks per week) or caffeine (greater than 300 mg/day), there was evidence of an association with ETS (adjusted OR around 3), indicating the possibility of interaction or a more susceptible subgroup.

3.3.3 Animal Studies of Perinatal Mortality and Tobacco Smoke Exposure

Information on perinatal mortality in animals is provided by endpoints such as: numbers of resorptions; number of live and dead fetuses at term (in studies with term hysterotomy), and litter size (in studies with spontaneous birth). Studies using mainstream smoke (see Table 3.7) were not generally supportive of effects on these parameters.

In the three available studies using sidestream smoke (SS) (Table 3.7), one study (Witschi *et al.*, 1994) found statistically significant effects of SS exposure on both the number of implantation sites per litter and the number of live pups per litter; this suggests that the primary effect was on implantation. The other two studies (Leichter, 1989; Rajini *et al.*, 1994) did not find effects of SS exposure on variables related to perinatal mortality.

3.3.4 Discussion and Conclusions

Relatively few studies have examined the association of ETS exposure and perinatal death. Two early studies (Comstock and Lundin, 1967; Mau and Netter, 1974) that examined neonatal mortality rates by paternal smoking status suggested an increased risk on the order of 50%. A third study (Yerulshalmy, 1971) did not present enough data for satisfactory interpretation, but suggested a possible effect of paternal smoking on neonatal death rates in LBW infants. The data with respect to stillbirth are even more sparse, but are not indicative of an association.

Two more recent studies of spontaneous abortion and ETS exposure (Windham *et al.* 1992; Ahlborg and Bodin, 1991) offer better data, although the exposure assessments were still somewhat crude, based only on questionnaire responses. Both studies reported an association of spontaneous abortion with ETS exposure, also on the order of 50%, although in one study the association was observed only with workplace, not home, exposure. One consideration in examining the relationship of fetal loss to paternal smoking is that it could reflect a direct effect of smoking on the sperm (if losses are due to fetal abnormalities), rather than an effect of ETS exposure to the mother and fetus. The two more recent studies of spontaneous abortion were based not only on paternal exposure, but also included other sources of ETS exposure. The finding in these two studies of a similar association of spontaneous abortion with ETS exposure as with active smoking may be difficult to reconcile with a causal association, given the lower levels of biomarkers measured in nonsmokers exposed to ETS and the fact that active smokers are also exposed to ETS. However, Remmer (1987) has suggested that enzyme induction of mono-oxygenase systems among active smokers leads to detoxification of toxic compounds; because such enzyme induction would probably not occur with the lower exposures of those exposed only to ETS, their fetuses are less protected.

In the three animal studies of the effects of sidestream smoke on variables related to perinatal mortality, results are indicative of an effect in only one (Witschi *et al.* 1994); studies using mainstream smoke were not generally supportive of an effect on these variables. Based on this limited information, it appears that measures reflecting perinatal mortality in animals are not particularly sensitive to gestational tobacco smoke exposure.

In conclusion, there is some epidemiologic evidence that ETS exposure may play a role in the etiology of spontaneous abortion, which is consistent with some but not all studies of active smoking. More work is needed because of the few studies available and the inconsistent findings.

3.4 Congenital Malformations

Congenital malformations include a wide variety of diagnoses, such as neural tube defects (*e.g.*, anencephaly, spina bifida), cleft palate, and defects of the genitourinary and the cardiovascular systems, among others. About two to three percent of births are generally considered affected. However, this may vary across studies, because some defects are not detectable at birth and thus would not be included in studies that did not ascertain defects later in infancy. Some studies limit cases to major malformations, whereas others use a broader definition of anomaly. There is some controversy about how to categorize diagnoses, *e.g.*, by organ system or embryologic origin. Potential confounding variables are not well-defined, but maternal age, prior reproductive history and socio-economic status should be considered.

3.4.1 Overview of Human Studies of Congenital Malformations and Maternal Smoking During Pregnancy

The literature on the relationship of active maternal smoking to congenital malformations is inconsistent. Some studies have found associations (Kelsey *et al.*, 1978; Himmelberger *et al.*, 1978), including with neural tube defects (see Little and Elwood, 1990) and oral clefts (Saxen, 1974; Khoury *et al.*, 1987), but others have not (Werler *et al.*, 1990; Kallen, 1989; Seidman *et al.*, 1990). The 1980 Surgeon General's report found there was insufficient data to support a judgment about whether parental smoking increases the risk of malformations (U.S. DHHS, 1980). A number of the papers cited above (and below) were published subsequent to that report, but do not present a stronger case, except perhaps for oral clefts.

3.4.2 Human Studies of Congenital Malformations and ETS Exposure

A half dozen studies have examined the potential association of prenatal ETS exposure and congenital malformations (Table 3.6); all published studies were based on paternal smoking status only. Thus any association seen may be due to a direct effect of smoking on sperm, rather than due to ETS exposure of the mother. Some studies have suggested that active smoking might cause genetic damage to the sperm as reflected by alterations in sperm parameters (Evans *et al.*, 1981; Marshburn *et al.*, 1989). Although little work has been done associating sperm parameters with pregnancy outcome, genetic damage could theoretically lead to a birth defect. Given the controversial nature of the data on the

association of maternal active smoking and congenital malformations, we also present those results with the studies reviewed that looked at both maternal and paternal smoking.

Mau and Netter (1974)

Mau and Netter (1974) looked at the incidence of malformations in their prospective study of pregnancy and child development (see Section 3.3.2). The rates of severe malformations among all newborns increased with amount smoked by the father: rates were 0.8 percent among those whose fathers did not smoke, 1.4 percent among those whose fathers smoked 1-10 cigarettes per day, and 2.1 percent among those whose fathers smoked more than 10 cigarettes per day ($p<0.01$). We calculated a crude odds ratio of 2.6 (95% CI= 1.5 - 4.7) for infants of fathers smoking more than 10 cigarettes per day (Table 3.6). The authors stated that the increase in risk was similar in surviving children and independent of maternal or paternal age, socioeconomic status and the participating clinic. No association was found with maternal smoking; deleting maternal smokers from the analysis did not change the results for paternal smoking. The increased risk was observed for specific categories of defects, namely, facial clefts (RR=7.0), neural tube defects (RR=1.7) and cardiac defects (RR=1.9). These categories included very small numbers, and only the elevated risk of clefts was statistically significant. An increased risk was also observed for multiple malformations (RR=3.3).

Holmberg and Nurminen (1980)

A case-control study of central nervous system defects designed to examine occupational factors (Holmberg and Nurminen, 1980) also reported on parental smoking. Cases were identified from the Finnish Register of Congenital Malformations for the years 1976-1978 and controls comprised the live birth immediately preceding the case born in the same district. A questionnaire was administered to mothers of cases and controls within a few months of delivery. Based on a matched analysis, we calculated an odds ratio of 1.3 (95% CI= 0.74 - 2.5) for paternal smoking, restricted in the interview to "the time when the woman became pregnant". Maternal smoking showed a greater association (OR=2.1, 95% CI= 1.0 - 4.4), but the authors reported that this association was diminished when adjusted for solvent exposure. No confounders were considered in the analysis of paternal smoking.

Hearey et al. (1984)

In a very small case-control study of neural tube defects initiated to investigate an identified cluster, Hearey *et al.* (1984) examined a wide variety of possible risk factors. Both mothers (n=36) and fathers (n=25) were interviewed. Paternal smoking was the only variable found significantly associated with the defects. The odds ratio for paternal smoking during the six months before conception or the first trimester was 16.0 (95% CI= 1.1 - 230.7). No adjustment for other factors, including maternal smoking, was made. The authors noted that the association was not significant in the matched analysis, nor in the time period restricted to only the six months before conception. The latter observation may actually make a stronger case for an ETS effect, because if the excess is associated

with paternal smoking during pregnancy (rather than prior to conception), the possibility of an effect on sperm is precluded.

Seidman et al. (1990)

Seidman *et al.* (1990) examined parental smoking and congenital malformations using data from the Jerusalem Study of Oral Contraceptive Use. Over 15,000 women who delivered between 1974 and 1976 were interviewed within a few days postpartum. Focusing on only the results for nonsmoking mothers, the authors noted nonsignificant increases in rates of minor and major malformations associated with heavy paternal smoking. The odds ratio we calculated for paternal smoking of greater than 30 cigarettes per day shows only a very slight elevation in the rates of minor malformations and a moderately elevated association with major malformations (Table 3.6). The authors reported that a multiple regression analysis revealed no significant associations with paternal smoking, but did not publish the results. In the regression analysis, maternal smoking was not associated with the incidence of either major or minor malformations. However, among older women (≥ 35 years) the malformation rates were elevated two-fold in smokers. The rates of some specific defect categories (spina bifida and genitourinary system defects) were non-significantly elevated among infants of maternal smokers, but data were not presented by defect category for paternal smoking**.**

Savitz et al. (1991)

Savitz *et al.* (1991) analyzed data from the large Child Health and Development Studies of Kaiser Births from 1959-66 with respect to the influence of paternal variables on the incidence of congenital anomalies. Congenital anomalies were broadly defined and were ascertained up to five years after birth. The association with paternal smoking was examined for over 30 categories of defects, so some were based on small numbers. Prevalence odds ratios (POR) adjusted for maternal variables were greater than 1.5 for four diagnoses: cleft lip with or without cleft palate; hydrocephalus, a nervous system defect; ventricular septal defect, a cardiovascular system defect; and urethral stenosis (Table 3.6). All of the confidence intervals were wide and included unity. A dose-response relationship for smoking one pack or more per day was suggested only for the clefts and urethral stenosis. A number of diagnoses had associations with a POR less than 0.7, including neural tube defects and patent ductus arteriosus, a cardiovascular defect. In these analyses, maternal smokers were not excluded, but this variable was controlled in the logistic regression model. Unfortunately, the number of unaffected births by exposure status was not provided, thus defects could not be grouped into broader diagnostic categories or by organ system for comparison to other studies.

Zhang et al. (1992)

Zhang *et al.* (1992) examined data on paternal smoking from a case-control study of birth defects conducted in Shanghai from 1986-87. Birth defects were ascertained within the first week of life or from pathology exams of perinatal deaths; controls were normal live births. Only two mothers reported smoking; they were excluded. Other confounders (*e.g.*, age, paternal drinking and chemical exposures) were not adjusted because their

occurrence was rare (<5%). The overall odds ratio of birth defects and paternal smoking was slightly elevated with little evidence of a dose-response effect (Table 3.6). Among 25 defect categories, elevated odds ratios were seen for pigmentary anomalies of the skin (3.3, 95% CI= 0.9 - 1.8), diaphragmatic hernia (2.3, 95% CI= 0.7 - 8.4), anencephaly (2.1, 95% CI= 0.9 - 4.9), spina bifida (1.9, 95% CI=0.7 - 5.4) and varus or valgus deformities of feet (1.8, 95% CI= 0.97 - 3.3). As can be seen, some confidence intervals were rather wide. The odds ratios for most other categories were greater than one. Exceptions were ventricular septal defect and other heart anomalies, polydactyly or syndactyly, hypoplasia of lung, or hypospadias; none of these were significantly below unity. For neural tube defect diagnoses (*e.g.*, anencephaly and spina bifida) alone, and in combination with other central nervous system defects (*e.g.*, hydrocephalus and microcephalus), we calculated ORs of 2.0 (95% CI= 1.1 - 3.7) and 1.6 (95% CI = 1.0 - 2.6), respectively. For some of the defects with elevated rates there was an indication of a dose-response relationship (*e.g.*, spina bifida, diaphragmatic hernia and the pigmentary anomalies). Classifying defects as isolated or multiple (in the affected individual) revealed a slightly greater association with multiple malformations, but no dose-response effect. The authors felt that confounding or reporting bias were unlikely to explain the observed results.

Shaw et al. (1993) and Wasserman et al. (1994)

A study recently reported at a scientific meeting (Shaw *et al.*, 1993) provided some data on parental smoking as well as other sources of ETS exposure. This case-control study of oral clefts found a dose-response association with amount of maternal smoking. Paternal smoking also appeared to show such an association, but not when maternal smokers were excluded. Thus, paternal smoking appeared to interact with maternal smoking. Exposure to others' smoke at work, or at places other than home, led to slightly increased risks among infants of maternal nonsmokers (OR = 1.5, 95% CI = 0.95 - 2.2, and OR=1.3, 95% CI = 0.88 - 1.8, respectively), as well as among smokers. These data are preliminary and not adjusted for co-covariates (and thus are not included in the tables). The findings for home (*e.g.*, paternal smoking) and workplace exposure are inconsistent, but the latter are indicative of a slight association with ETS.

A more recent presentation from the same investigators (Wasserman *et al.*, 1994) provided data on parental smoking and neural tube defects and conotruncal heart defects. An increase in the ORs for the heart defects was seen when both parents smoked (crude ORs ranged from 1.4 to 2.0 by amount smoked), but not when only one smoked. Little consistent pattern of risk with parental smoking was noted with neural tube defects, in contrast to the published studies discussed above. Information on workplace exposure was not presented.

3.4.3 Animal Studies of Congenital Malformations and Tobacco Smoke Exposure

Malformations in animals are detected in term fetuses by gross examination, soft tissue examination via dissection and skeletal examination after staining; a complete teratology study includes all three exams. Of seven studies of mainstream smoke using one or more

of these techniques, four did not find any effects (Wagner and Chouroulinkov, 1972; Reznik and Marquard, 1980; Peterson, 1981; Bassi *et al.*, 1984) and three mentioned limited findings (Schoeneck, 1941; Tachi and Aoyama, 1983; Amankwah *et al.*, 1985) but did not provide enough information for evaluation or for characterization of defects.

Of the three available sidestream smoke studies, one (Witschi *et al.*, 1994) did not examine malformations. Using gross examination only, Leichter (1989) reported no effects. Rajini *et al.* (1994) reported finding no effects using gross and skeletal examinations, but did no soft tissue examination. Thus no complete teratology study has been conducted with sidestream smoke.

3.4.4 Discussion and Conclusions

Although the epidemiologic studies reviewed suggest a moderate association of severe congenital malformations with paternal smoking (with odds ratios from 1.2-2.6 for all malformations combined, or for major malformations), none presented compelling evidence that ETS exposure causes congenital malformations. The use of paternal smoking status as a surrogate for ETS exposure means that a direct effect of active smoking on the sperm cannot be ruled out. Several studies found greater associations with specific defects, but the defects implicated differed in different studies. The most consistent association appears to be with central nervous system or neural tube defects; this association was observed in all but one study (Savitz *et al.*, 1991) of the five that provided sufficient data. Due to the limitations in assessing exposure in the existing studies, it is not possible to determine whether there is an association of ETS exposure with birth defects.

None of the studies currently published had information on ETS exposure from multiple sources (*e.g.*, home and work), nor did any include measurement of a biomarker. Thus, an association will be more difficult to detect if there is misclassified exposure such that the comparison group includes pregnancies exposed to ETS from sources other than the spouse. Given that the results of studies of active smoking have been inconsistent, a teratogenic effect of ETS is unlikely to be strong; it would be very difficult to detect a significant association of a weak teratogen which occurs at such low levels with outcomes as rare as specific birth defects. Furthermore, because of the relative dearth of information on causes of malformations, it is difficult to determine whether confounding variables have been adequately controlled.

In animals, the three available sidestream smoke studies found no effects; however, no complete teratology study has been conducted. Results of only three of seven studies of mainstream smoke suggest an association (Shoeneck, 1941; Tachi and Aoyama, 1983; Amankwah *et al.*, 1985). Based on this limited information, measures of congenital malformations in animals do not appear to be sensitive to tobacco smoke exposure.

In conclusion, at this time it is not possible to determine whether there is an association of ETS exposure with birth defects.

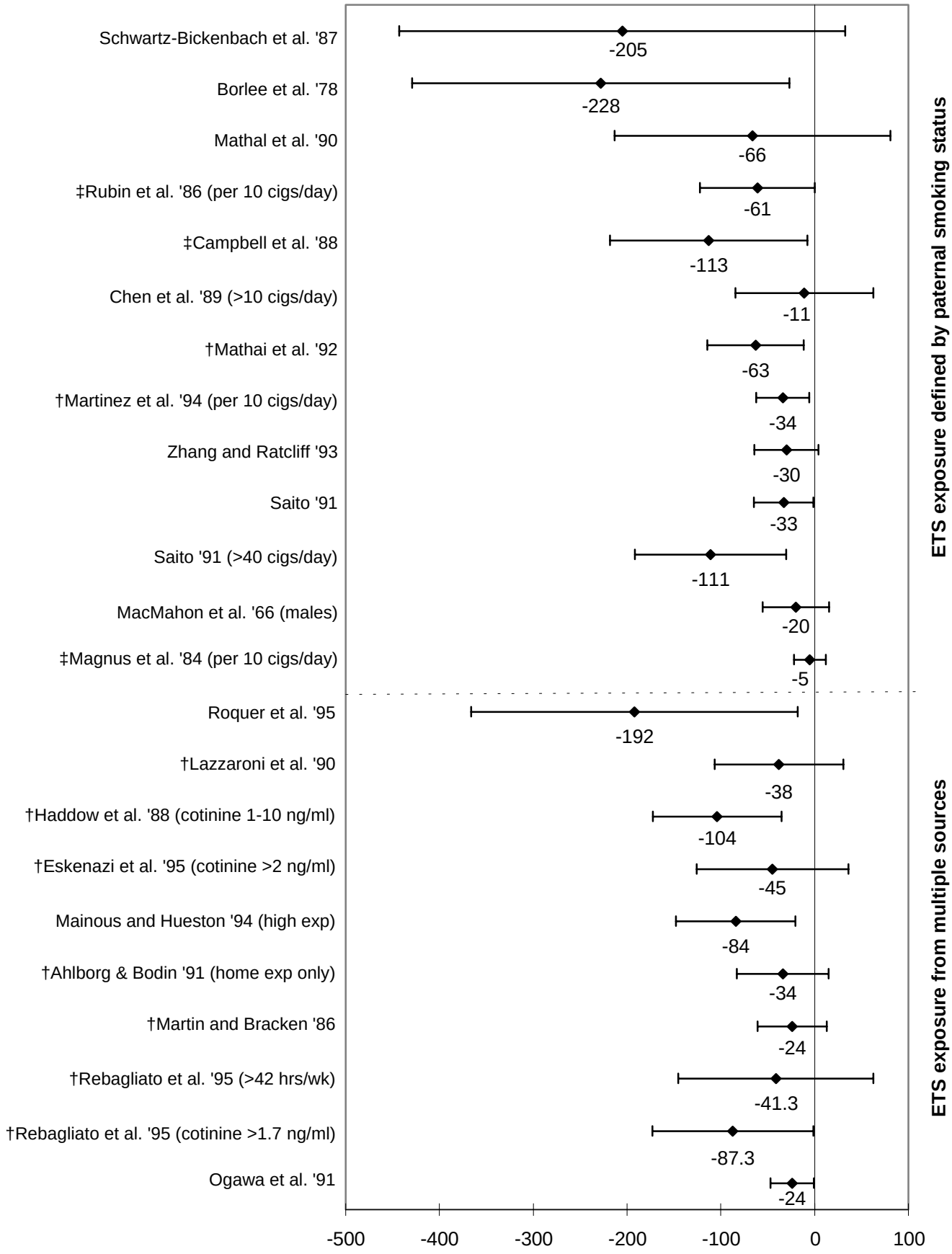
3.5 Chapter Summary and Conclusions

More than twenty-five epidemiologic studies of the relationship between fetal growth and ETS exposure were reviewed. All but one of the studies that examined mean birthweight found a decrement with ETS exposure, although some of the weight differences were small. A few early studies found little effect, but none of them controlled for confounders or performed rigorous statistical analyses. The majority of studies which examined the endpoints low birthweight or small for gestational age have shown a slightly elevated risk (20-40%) with ETS exposure. Current epidemiologic studies, with support from animal studies and the known association with active smoking, provide sufficient evidence that ETS exposure adversely affects fetal growth. The primary effect is a reduction in birthweight that is of a small magnitude (25-50 grams), and may not be clinically significant for an individual infant at low risk. Yet, if the entire birthweight distribution is shifted lower with ETS exposure, as it appears to be with active smoking, infants who are already compromised may be pushed into even higher risk categories. Low birthweight is associated with many well-recognized problems for infants and is strongly associated with perinatal mortality.

Of the relatively few studies that have examined the association of ETS exposure and perinatal death, early studies suggest an increased risk of neonatal mortality rates associated with paternal smoking. The data with respect to stillbirth are more sparse, but are not indicative of an association. Two modern studies reported an association of spontaneous abortion and ETS exposure from multiple sources, although in one study the association was observed only with workplace, not home, exposure. These, as well as two weaker studies, provide some epidemiologic evidence that ETS exposure may play a role in the etiology of spontaneous abortion, but further work is needed, particularly as a recent report did not confirm these findings.

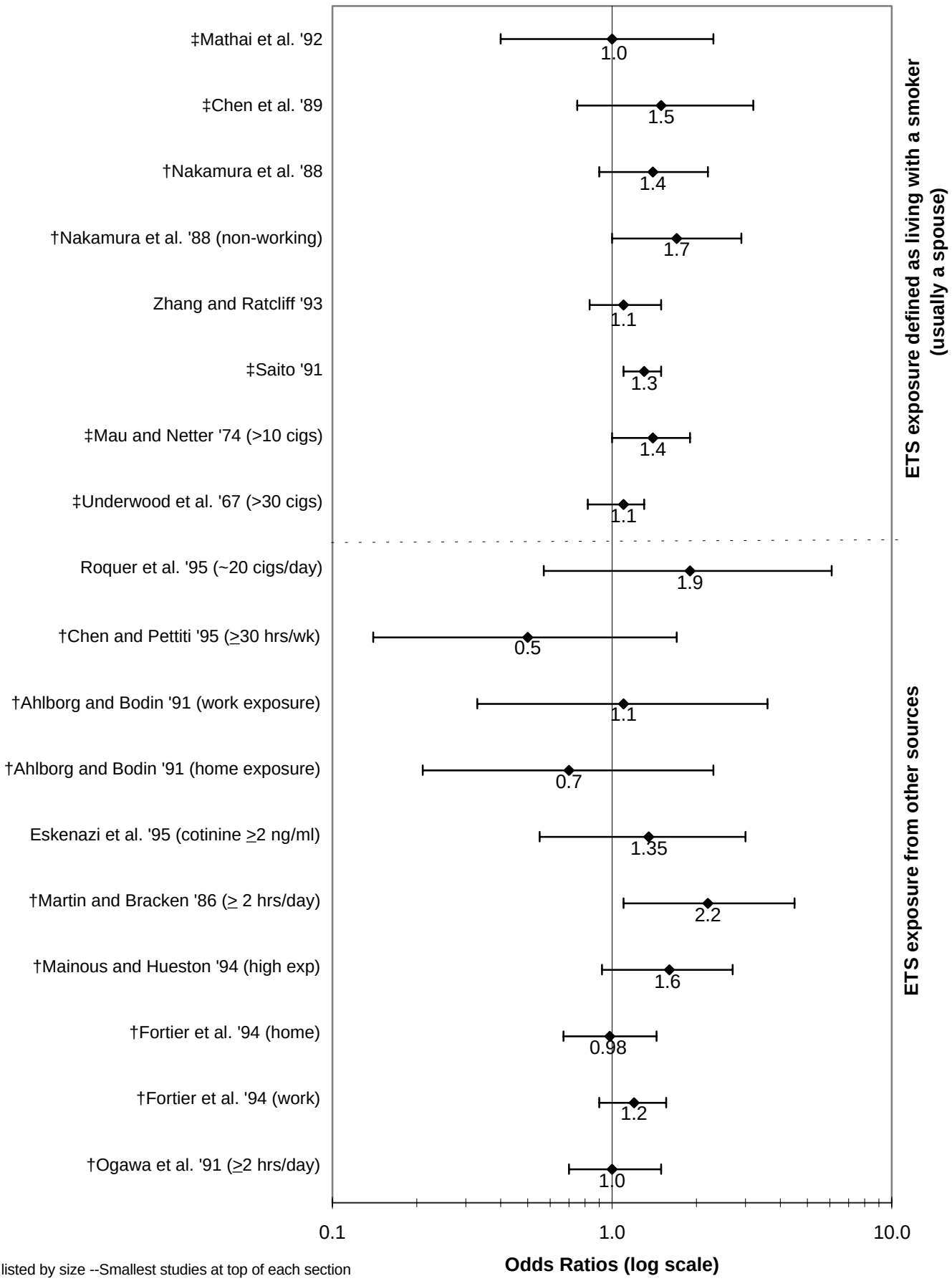
Although the epidemiologic studies reviewed suggest a moderate association of severe congenital malformations (birth defects) with paternal smoking, none presented compelling evidence that ETS exposure causes congenital malformations. The use of paternal smoking status as a surrogate for ETS exposure means that a direct effect of active smoking on the sperm cannot be ruled out. Several studies found associations with specific defects, but the defects implicated differed in different studies. The most consistent association appears to be with central nervous system or neural tube defects; this association was observed in all but one of the five studies that provided sufficient data. Due to the limitations in assessing exposure in the existing studies, it is not possible to determine whether there is an association of ETS exposure with birth defects.

Figure 3.1 Summary of Differences in Mean Birthweight and 95% Confidence Intervals between ETS-Exposed and Unexposed Pregnancies by ETS Definition and Study Size*



* Studies listed by size --Smallest studies at top of each section
† Adjusted
‡ All women (includes smokers), adjusted

Figure 3.2 Odds Ratios and 95% Confidence Intervals for the Association of Low Birthweight (or IUGR) and ETS, by ETS Definition and Study Size*



* Studies listed by size --Smallest studies at top of each section
† Adjusted
‡ OR and CI calculated from data, sometimes estimated

TABLE 3.1
STUDIES OF BIRTHWEIGHT AND ETS EXPOSURE DEFINED BY PATERNAL SMOKING STATUS

Authors (year) Country	Study Design	Difference in Mean Birthweight by Exposure[1]
MacMahon *et al.* (1966) US (Massachusetts)	Retrospective mail questionnaire (12,192 white singletons) (5,935 maternal nonsmokers)	-22g (-57, 13) females -20g (-55, 15) males -28g for pipe/cigar (n.s.) no consistent effect by amount
Comstock & Lundin (1967) US (Maryland)	Special census linked to vital records (448 births)	-42g (no statistics provided)
Underwood *et al.* (1967) Worldwide	Naval records of labor and delivery; cross-sectional (48,505 singletons with 24,674 maternal nonsmokers)	-7 to -3g, by amount smoked
Borlee *et al.* (1978) Belgium	Retrospective interview (175 normal live births, 202 malformed)	-228g (-429.0, -26.7) crude (p = 0.06 for paternal smoking impact analysis that controlled for maternal smokers)[2]
Magnus *et al.* (1984) Norway	Retrospective interview of twins (parents of offspring studied) (3130 families; 5,188 births)	regression for categories of about 10 cigs/day: crude: -48g (-65, -31) adjusted for maternal smoking[2]: -5g (-23, 13)
Rubin *et al.* (1986) Denmark	Interview at delivery (500 term live births >2000g)	adjusted for maternal smoking: -6.1g/cig (-12, -0.2)[2] -120g/pack
MacArthur & Knox (1987) England	Unknown (180 mothers who quit smoking in pregnancy)	-14g crude not significant in an analysis for the effect of paternal smoking

[1] All effect measures assessed in non-smoking mothers unless otherwise specified (e.g., "smoking adjusted"). All 95% confidence intervals calculated by reviewers from available data. n.s. = not statistically significant (p>0.05).

[2] Control for at least some confounders (see text discussion of studies).

[3] Based on living with a household smoker, not only the spouse.

TABLE 3.1 (continued)
STUDIES OF BIRTHWEIGHT AND ETS EXPOSURE
DEFINED BY PATERNAL SMOKING STATUS

Authors (year) Country	Study Design	Difference in Mean Birthweight by Exposure[1]
Schwartz-Bickenbach *et al.* (1987) Germany	Interview at delivery (54 pairs-smoke and not, followed while breast-feeding)	-205g (-440, 30.1), crude
Campbell *et al.* (1988) England	Interview 1 month post-delivery (518 white singles)	-113g (-216, - 8)[2] (from regression after adjusting for maternal smoking)
Brooke *et al.* (1989)[3] England (London)	Prospective interview (1513 white births with 1,018 nonsmokers)	-18g or 0.5% reduction[2] (p = 0.56)
Chen *et al.* (1989)[3] China (Shangai)	Retrospective mail questionnaire (1,058 births)	-11g (-81.9, 64.1) paternal smoking ≥10/day -15g (-94.5, 64.5) any other smokers ≥10/day adj made no difference[2] no dose effect
Saito (1991) Japan	Interview at infant care visit (3,000 couples)	smoke any: -33.4g (-66.3, -0.5) For ≥ 40 cigs/day: -111g (-191.0, -31.7), crude
Mathai *et al.* (1990)[2] England (Liverpool)	Prospective interview (285 white singles)	-66g (-213.0, 81.1), crude
Mathai *et al.* (1992) India (Vellore)	Interview (994 singletons)	-63g (-114g, -12)[2]
Zhang & Ratcliffe (1993) China (Shangai)	Interview post-delivery (1,785 singleton term births)	-30g (-66,7)[2] -62g for 15-19 cigs/day but + 32 for ≥ 20/day
Martinez *et al.* (1994) US (Arizona)	Interview at delivery (1219 births, 907 nonsmokers)	-34g (-63, -5)[2] per 10 cigarettes

[1] All effect measures assessed in non-smoking mothers unless otherwise specified (e.g., "smoking adjusted"). All 95% confidence intervals calculated by reviewers from available data. n.s. = not statistically significant (p>0.05).

[2] Control for at least some confounders (see text discussion of studies).

[3] Based on living with a household smoker, not only the spouse.

TABLE 3.2
STUDIES OF FETAL GROWTH AND ETS EXPOSURE AT HOME DEFINED BY PATERNAL SMOKING STATUS

Study		Odds Ratios (95% CI)[4]		
Authors (year) Location	**Study Design**	**Low Birth Weight (LBW)**	**IUGR/SGA**	**Preterm**
Underwood *et al.* (1967)[1] Worldwide	Naval records of labor and delivery (24,674 nonsmoking mothers)	0.9 (0.8, 1.0) any 1.05 (0.82, 1.3) >30 cigs	- -	0.9 (0.8, 1.0) any 1.05 (0.8, 1.3) >30 cigs
Yerulshalmy (1971)[1] US (N. California)	Prospective study of Kaiser members (9,793)	0.9 (n.s.) mother nonsmoker 1.4 (p<0.05) mother smoker	- -	- -
Mau & Netter (1974)[1] Germany	Prospective interview (5,183; 3,696 nonsmokers)	1.4 (1.0, 1.9) >10 cigs/day	1.2 (0.9, 1.7) >10 cigs/day	1.2 (0.9, 1.6) >10 cigs/day
Nakamura *et al.* (1988) Japan (Osaka)	Prospective interview (2,371 nonsmokers)	1.4 (0.9, 2.2)[3] ---------- In non-working women: 1.7 (1.0, 2.9)[3]	1.2 (0.8, 2.0) ---------- 1.4 (0.8, 2.4)	1.2 (0.8, 1.8) ---------- 1.1 (0.7, 1.8)
Chen *et al.* (1989)[1,2] China (Shanghai)	Retrospective, self-administered (1,163)	1.5 (0.75, 3.2)	- -	- -
Saito (1991)[1] Japan (Osaka)	Retrospective interview (3,000 couples)	- -	1.3 (1.1, 1.5)	1.0 (0.8, 1.3)
Mathai *et al.* (1992)[1,2] India	Interview, but timing unclear (994)	1.0 (0.4, 2.3) (LBW defined as <2000g)	- -	1.6 (0.8, 2.9)
Zhang & Ratcliffe (1993) China (Shanghai)	Interview post-delivery (1,785 term births of nonsmokers)	- -	1.1 (0.83, 1.5)	- -

[1] Odds ratios and/or confidence intervals estimated from published data, not published by original authors.

[2] Based on any household smoker, instead of only paternal smoker.

[3] Controlled for confounders.

[4] n.s. indicates lack of statistical significance at p = 0.05.
IUGR - Intrauterine Growth Retardation; SGA - small for age gestational; LBW at term.

TABLE 3.3
STUDIES OF FETAL GROWTH AND ETS EXPOSURE
OF MATERNAL NON-SMOKERS FROM MULTIPLE ETS SOURCES

Study		Results[2]	
Authors (year) Country(study size [1])	**ETS Level (% Exposed)**	**Difference in Mean Weight**	**IUGR/LBW OR (95% CI)**
Martin & Bracken (1986) US (Connecticut) (n=2,473) Prospective interview	≥ 2 hr/day at home or work (34%)	-24 g adjusted (-60,13) -85 g (p<0.002) crude	2.2 (1.1-4.5) LBW
Ogawa *et al.* (1991) Japan (n=5,336) Interview around delivery	≥ 2 hr/day at home, work or elsewhere (35%)	-10.8 g (n.s.) -24 g (-47, -2) crude	1.0 (0.7-1.5) LBW
Lazzaroni *et al.* (1990) Italy (n=648; examined births >2000g, ≥ 37 wks gestation) Interview postpartum	≥ 1 hr/day at home or work (25%)	-38 g (-106.9, 30.7) -17 g/hr (-35, 1.3)	- -
Ahlborg & Bodin (1991) Sweden (n=2,461 employed) Interviewed during month 2 or 3 of pregnancy	Home exposure only (16%) ---------- Most time at work in rooms with smokers (11%)	-34 g (-82, 15) (very small numbers) ---------- 20 g (-37, 77)	0.7 (0.21-2.3) LBW (based on 3 infants) ---------- 1.1 (0.33-3.6) LBW 1.4 (0.33-5.9) LBW if worked full-time
Fortier *et al.* (1994) Canada (Quebec) (n = 4,644 non smokers) Interview within few months post partum	Home only (13%) ---------- Work only (28%) ---------- Home and Work (8%)	 ---------- ---------- 	0.98 (0.67- 1.44) IUGR ---------- 1.18 (0.90-1.56) IUGR ---------- 0.94(0.60-1.49) IUGR

1 The study size (n) presented is for term births to nonsmokers, not the total study size.

2 Effect measure adjusted for a number of confounders, unless otherwise indicated as "crude". Abbreviations: LBW - low birth weight; IUGR - intrauterine growth retardation.

3 The analysis adjusted for LBW in previous births. This may result in substantial under estimation of effect.

TABLE 3.3 (continued)

STUDIES OF FETAL GROWTH AND ETS EXPOSURE OF MATERNAL NON-SMOKERS FROM MULTIPLE ETS SOURCES

Study		Results	
Authors (year) Country (study size[1] ETS Ascertainment	**ETS Level (% Exposed)**	**Difference in Mean Weight**	**IUGR/LBW[3] OR (95% CI)**
Mainous & Hueston (1994) US (nationwide) (n=3,253) Retrospective survey	Categorized as: never (23%) occasional (46%) often (17%) always (13%)	-84g (-150, -18) for highest exposure, crude No decrement at lower levels	1.6 (0.92, 2.7) LBW with high exposure ($p \leq 0.01$ dose response trend)
Chen & Petitti (1995) US (California) (n=111 cases, 124 controls, whites) Retrospective interview	Assessed in 4 locations and as average hrs/week Any exposure (54%) ≥30 hours/wk (7%)	- -	≥30 hrs/week: 0.5 (0.14, 1.7) IUGR work only: 1.0 (0.39, 2.6) IUGR home only: 0.5 (0.13, 1.8) IUGR
Roquer *et al.* (1995) Spain (n=129) Interview at delivery	"Significant" defined as exposed to ≥20 cigarettes/day	-192 (-365, -19), crude	1.9 (0.57, 6.1) 1.10 IUGR 1.11 crude
Rebagliato *et al.* (1995) Spain (n=710) Interview in 3rd trimester	Assessed hours per week from 4 sources Any exposure (88%) ≥42 hours/week (22%)	Any: -85g, crude any ≥42 hours/wk: -41g (-144, 61)[2] spouse ≥42hrs/wk: 31g (-103, 165)	- -

1 The study size (n) presented is for term births to nonsmokers, not the total study size.

2 Effect measure adjusted for a number of confounders, unless otherwise indicated as "crude".
Abbreviations: LBW = low birth weight; IUGR = intrauterine growth retardation.

3 The analysis adjusted for LBW in previous births. This may result in substantial under estimation of effect.

TABLE 3.4
STUDIES OF FETAL GROWTH AND ETS EXPOSURE DETERMINED BY BIOMARKERS

Study			Results	
Authors (year) Location	**Design (size)**	**Biomarker Levels[1]**	**Weight Difference**	**Low Birth Weight**
Hauth *et al.* (1984) US (Texas)	Maternal serum at labor Cord blood at delivery (163; 134 nonsmokers)	Mean in ETS = 26 ± 2.5 umol/L SCN vs. 23 ± 1.5 in nonsmokers cord blood (n.s.)	Correlation of wt and SCN = -0.74 in smokers ($p<0.001$) vs. r = 0.02 in ETS exposed, r = 0.15 in nonsmokers	--
Haddow *et al.* (1988) U.S. Maine	Serum drawn early in 2nd trimester (1231 nonsmokers)	1-10 ng/ml cotinine vs. <0.5 in nonsmokers	-104 g (adj.) (-173,-35) -28 g/ng/ml cotinine (CI = -55, -2,)	"rate ↑ 29%" (e.g., OR : 1.29) no statistics or numbers provided
Mathai *et al.* (1990) England	Urine at 16 weeks (285; 184 nonsmokers)	Mean in ETS = .85 ± 2.8 vs. .29 ± 1.4 µg cotinine/mg creatinine in nonsmokers	-25 g/µg cotinine/mg creatinine (p0.001) (includes smokers)	--
Eskenazi *et al.* (1995) U.S. (California)	Serum in 2nd trimester, stored for 25 years (3,578; 2,292 nonsmokers)	2 - 10 ng/ml cotinine versus <2 ng/ml continuous cotinine level	-45g (adj.) (-126, 36) inclding smokers: 1g per ng/ml cotinine (adj.) (-1.14, -0.79)	1.35 (0.60, 3.0) crude
Rebagliato *et al.* (1995) Spain	Saliva in 3rd trimester (n=710 nonsmokers)	≤ 0.5 = unexposed Quintiles of cotinine (Mean in ETS exposed = 1.2 ng/ml)	Any: -35g, crude Highest quintile (>1.7ng/ml): -87g, (adj.) (-174, -1)	- -

[1] Abbreviations: SCN = thiocyanate, CI = confidence interval, OR = odds ratio, r = correlation coefficient.

TABLE 3.5
ETS EXPOSURE IN RELATION TO SPONTANEOUS ABORTION AND PERINATAL DEATH[1]

Authors (yr) Location	Design (study size)	Exposure Definition	Results	Comments
Comstock & Lundin (1967)[2] Maryland	Sample from special census, vital records (n = 234 still births, 158 neonatal)	Paternal smoking (non-smoking mother)	RR = 1.45 (0.9-2.4) for NM. No effect on SB. (noted increased NM in small group where mom started smoking after pregnancy).	Adjusted for infant sex and patient education only. Exposure not specific to pregnancy. Completeness of FD records?
Mau & Netter (1974)[2] Germany	Interview in early pregnancy (n = 5,183)	Paternal smoking by amount (>10 cigs/day)	RR of perinatal death = 1.5 (C.I.= 1.1-2.3) RR for SB = 1.2 (n.s.) RR for SAB = 1.1 (n.s.)	Considered confounders, but RR not adjusted. Methods sketchy. No dose response.
Lindbohm *et al.* (1991) Finland	Case-control study of SABs in lead-monitored men and wives (n=213 SABs, 300 controls)	Paternal smoking status	OR for SAB = 1.3 (0.9-1.9)	Not adjusted. Includes maternal smokers. Generalizability?
Ahlborg & Bodin (1991) Sweden	Prospective questionnaire (n = 4,687 pregnancies)	"Live with smoker." Most time at work with smokers (non-smoking mother)	RR for SAB + SB and ETS at home = 1.0 at work = 1.5 (0.98-2.4) RR = 2.2 (1.2-3.8) for early SAB & work ETS.	Adjusted. Work exposure more intense.
Windham *et al.* (1992) California	Case-control (n = 626 SABs, 1,300 births)	≥ 1 hr/day (yes/no) in first 20 weeks. Paternal smoking (non-smoking mother)	OR for SAB = 1.6 (1.2-2.1) late SAB (> 12 wks) OR = 1.9 (1.4-2.7)	Adjusted. No effect of paternal smoking when adjusted.

1 Includes stillbirth or fetal death and neonatal mortality.

2 Odds ratios and confidence intervals calculated from data, not by original authors.

Abbreviations: SAB = spontaneous abortion, SB = stillbirth, NM = neonatal mortality, FD = fetal death, RR = rate ratio, OR = odds ratio.

TABLE 3.6
ETS EXPOSURE AND CONGENITAL MALFORMATIONS

Authors (yr) Location	Design (study size)	Exposure Definition[1]	Results	Comments
Mau & Netter (1974)[2] Germany	Interview in early pregnancy (n = 5,183)	Paternal smoking by amount (>10/day)	RR for severe BD = 2.6 (1.5-4.7) RR for facial clefts = 7.0 (p<.05) Cardiac defects = 1.9 (n.s.) NTDs = 1.7 (n.s.)	Looked at some confounders, but not adjusted. Little information on methods.
Holmberg & Nurminen (1980) Finland	Case-control, registry based (n = 120 CNS anomalies & 120 cntrls)	Paternal smoking at conception	OR = 1.3 (0.74-2.5)	Not adjusted. Includes maternal smokers.
Hearey *et al.* (1984) California	NTD cluster, case-cntrl (n = fathers of 8 cases & 17 controls) Retrospective interview	Father smoke peri-conceptional (father interviewed)	OR = 16.0 (p<0.05) unmatched	Not adjusted. (Includes maternal smokers.) n.s. in matched analysis. Small numbers.
Seidman *et al.* (1990)[2] Israel	Interview post-partum (n = 17,152 infants)	Paternal smoking (amount)	RR = 1.45 (0.73 - 2.8) for >30 cigs/day[2] and major BDs. RR = 1.1 (0.85, 1.5) for minor BDs.	Multivariate adjustment (results not shown). Little dose-response. Effect of maternal smoking seen in older women only.
Savitz *et al.* (1991) California	Prospective in HMO members (Child Health & Development Study) (n = 14,685 births)	Paternal smoking at prenatal interview	OR = 2.4 (n.s.) for hydrocephalus OR = 2.0 for VSD and urethral stenosis (n.s) OR = 1.7 for CLP (n.s.) OR = 0.6 for NTDs (n.s.)	Multivariate adjustment includes smoking mothers. Multiple comparisons. Little dose response.
Zhang *et al.* (1992)[2] China	Case-control interview in hospital (n = 1012 cases, 1012 controls)	Paternal smoking	RR = 1.2 (1.0 - 1.5) for all BD. Numerous types elevated, but n.s. RR = 1.6 for CP RR <1.5 for hydrocephalus RR <1.0 for VSD RR = 2.0 (1.1, 3.7)[2] for NTDs	Not adjusted but low-risk subgroup. Greater association with multiple vs. single defects. No dose-response. Multiple comparisons.

[1] Among non-smoking women unless otherwise specified. Exposure ascertained from mother unless otherwise specified.

[2] Confidence interval calculated by reviewer.

Abbreviations: BD = birth defects, NTD = neural tube defects, CNS = central nervous system, VSD = ventricular septal defect, CLP = cleft lip and/or cleft palate, CP = cleft palate, n.s. = not significant or p > 0.05.

TABLE 3.7
ANIMAL STUDIES OF TOBACCO SMOKE EXPOSURE AND FETAL GROWTH

Mainstream or Unidentified Type of Smoke

Authors (year)	Species	Exposure Period	Fetal Weight at Term
Essenberg *et al.* (1940)	rats	mating through lactation	"2/3rds under weight" (no statistics)
Younoszai *et al.* (1969)	rats	day 3 - 22 gestation	-16%
Wagner *et al.* (1972)	mice	day 11 - +16 days gestation	-16% (not significant)
Haworth & Ford (1972)	rats	day 3-20 gestation	-19%
Reckzeh *et al.* (1975)	rats	day 1-18 gestation	-6% (not significant)
Reznik & Marquard (1980)	rats	day 0-21 gestation	-31%
Peterson *et al.* (1981)	mice	day 6-17 gestation	-4% (not significant)
Bertolini *et al.* (1982)	rats	day 1-20 gestation	-9% (not significant)
Tachi & Aoyama (1983)	rats	day 0-21 gestation	-30%
Bassi *et al.* (1984)	rats	day 5-20 gestation	-21%
Amankwah *et al.* (1985)	mice	day 0 - birth	-4%
Rogers & Kuehl (1988)	baboons	"throughout pregnancy"	-17% (no statistics)

Sidestream Smoke

Authors (year)	Species	Exposure Period	Fetal Weight at Term
Leichter (1989)	rats	day 1-20 gestation	-9%
Witschi *et al.* (1994)	rats	day 3-10 gestation	0% (not significant)
Rajini *et al.* (1994)	rats	day 3, 6-10 and 13-17 gestation	-7%
Mohtashamipur *et al.* (1987) (abstract)	rats	"1st, 2nd and 3rd week of pregnancy"	"significant losses" no statistics

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